

Dietary Supplements and Military Divers

A Synopsis for Undersea Medical Officers



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January 2004**

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 01 JAN 2004		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE Dietary Supplements and Military Divers A Synopsis for Undersea Medical Officers				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Department of Military and Emergency Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited					
13. SUPPLEMENTARY NOTES The original document contains color images.					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 117	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

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I. Introduction

A. Overview of Nutritional Supplements

The variety, availability, sales and use of dietary supplements (DS) remain poorly understood by the mainstream medical community, but the potential for use and abuse of DS cannot be taken lightly by undersea medical officers (UMO). Despite the indisputable pharmacologic effects many of these over-the-counter (OTC) products exert, the use of DS is generally overlooked by clinicians. DS information is not covered in much depth, if at all, in medical education, and physicians are not trained in this area. As such, many may feel uncomfortable with their lack of familiarity regarding the ever-increasing supplement pharmacopoeia.

Peer-reviewed scientific research and evidenced-based information are often limited. Moreover, because the general public and active duty community perceive these natural substances as harmless, the products often do not come to the attention of physicians at all. Less than half of all users of DS consult a physician or a practitioner about alternative products (Aeromed)

Whereas the literature on DS use is limited, research specific to use of DS under extreme environments is even sparser: virtually no studies have been conducted in hyperbaric/undersea environments. Due to the physiologic and psychological challenges of these extreme environments, military and civilian restrictions on the use of most medications in aviation and diving are quite specific and very strict. Because DS are not regulated by the Food and Drug Administration (FDA) as drugs, specifics regarding their use have not been addressed in diving regulations. To date, US Navy divers are not required to disclose their use of supplements, nor has it been common practice for UMOs or civilian equivalents to inquire about such use. However, considerable risks are expected with the use of many DS that are currently marketed. The safety and efficacy of most DS are not known for environments encountered routinely by the military diver. The purpose of this manual is to allow the UMOs to become familiar with common DS and make appropriate clinical decisions in light of the physical and psychological stressors of the hyperbaric environment.

B. Concerns about Nutritional Supplements

Concerns about DS use in the diving community include limited research on safety and efficacy, ease of availability, questionable sources of information, unfounded and exaggerated claims, and the unique mental and physical demands of military missions. In addition, there is no requirement for pre-market safety or efficacy testing (Aeromed). Because DS cannot be patented, there is little interest or funding for research on efficacy. Highly customized preparations, multiple active ingredients by diverse names, lack of standardization, and performance advantages too small to be detected even in relatively large studies have hindered attempts at legitimate scientific research on DS (USARIEM TN-0114).

Although research progresses slowly, new products, new combinations and new claims grow almost exponentially. DS advertisements and infomercials inundate the media. Whereas the presence of health and nutrition stores on military installations may often be construed as endorsement of products, it is really targeted marketing aimed at a population whose high physical demands make them receptive to promises of weight loss, improved performance or recovery, or a host of other exaggerated, usually unfounded, claims. Additionally, the Internet, which is a tremendous source of up-to-date information on just about anything, is unregulated and unpoliced. It can be daunting, particularly for the layperson, unfamiliar with the tools to make such dif-

ferentiations or distinctions and to differentiate the moderately legitimate information from the quackery. Further influences come when celebrity athletes endorse, or even just reveal, personal DS usage (celebrity effect article). Thus, education by both UMOs and the undersea community on the topic of DS is absolutely critical.

C. The US Government and Dietary Supplements

For decades, the FDA regulated dietary supplements as foods, in most circumstances, to ensure that they were safe and wholesome and that labeling was truthful and not misleading. The 1958 Food Additive Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act) were a key regulation for ensuring safety of all new ingredients, including those used in dietary supplements. However, President Clinton signed the Dietary Supplements Health and Education Act (DSHEA) on October 25, 1994. The DSHEA acknowledged that consumers firmly believe that DS may help to augment daily diets and provide health benefits. With the passage of DSHEA, Congress amended the FD&C Act to include several provisions that apply only to dietary supplements and dietary ingredients of DS. As a result of these provisions, dietary ingredients used in DS are no longer subject to the pre-market safety evaluations required of other new food ingredients or for new uses of old food ingredients.

The provisions of DSHEA (1) define DS and dietary ingredients; (2) establish a new framework for assuring safety; (3) outline guidelines for literature displayed where supplements are sold; (4) provide for use of claims and nutritional support statements; (5) require ingredient and nutrition labeling; and (6) grant FDA the authority to establish good manufacturing practice (GMP) regulations. The law also required formation of an executive level Commission on Dietary Supplement Labels and an Office of Dietary Supplements within the National Institutes of Health. The FDA traditionally considered DS to be composed only of essential nutrients, such as vitamins, minerals, and proteins. The Nutrition Labeling and Education Act of 1990 added herbs, or similar nutritional substances, to the term dietary supplement. Through the DSHEA, Congress expanded the meaning of the term dietary supplements beyond essential nutrients to include such substances as ginseng, garlic, fish oils, psyllium, enzymes, glandulars, and mixtures of these.

The formal definition of dietary supplement established by DSHEA includes the following criteria: (<http://vm.cfsan.fda.gov/~dms/dietsupp.html> and <http://www.fda.gov/opacom/laws/dshea.html>)

- A product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.
- Intended for ingestion in pill, capsule, tablet, or liquid form.
- Not represented for use as a conventional food or as the sole item of a meal or diet.
- Labeled as a “dietary supplement.”
- Includes products, such as an approved new drug, certified antibiotic, or licensed biologic, that was marketed as a DS or food before approval, certification, or license (unless the Secretary of Health and Human Services waives this provision).

DSHEA, in effect, increased the amount of misinformation that can be disseminated to prospective customers and expanded the types of products that could be sold as DS. Since its passage, hormones, such as DHEA and melatonin, are promoted as DS. DSHEA does not require that

DS be shown as safe or effective before marketing, and the FDA does not evaluate DS prior to being made available to consumers. However, the FDA is permitted to restrict a substance if it poses a significant and unreasonable risk under the conditions of use on the label or as commonly consumed. This is what happened with Ephedra products, which were banned in December 2003. Also of note is the fact that the Federal Trade Commission (FTC) has jurisdiction over the advertising of DS. However, the FTC is far too small to control the DS industry, even though the threat of FTC action can ensure that some marketers are cautious.

II. Classes of Supplements

A. Energy Enhancers

1. Caffeine

Sources

Caffeine is present in the leaves, nuts or seeds of more than 60 species of plants. Many of the plants are listed as ingredients in dietary supplements. Caffeine, per se, need not be listed as an ingredient unless it has been added in addition to the food sources. The most common dietary/herbal sources of caffeine are coffee, tea, soft drinks, cocoa, guarana, maté, and cola nut.

DO NOT CONFUSE the above caffeine sources with the following similar-sounding herbs that DO NOT CONTAIN caffeine: coca leaf, guar gum, maca, and gotu kola.

More recent additions to the caffeine market include energy drinks (Red Bull, Piranha EAS, Bawls, Cricket Cola, and Whoop Ass), gels (Cliff SHOT, Gu, Carbo Shotz, PowerGel, Carb-BOOM!), candies (Penguin Mints, Jo Mints, Jolt Gum, XTZ Energy Truffles), Buzz Water caffeinated water, Sky Rocket caffeinated syrups, Shower Shock caffeinated bar soap, Polar Bear Snuff – a white powder mix of caffeine crystals and herbs snorted nasally. There are multiple other source of caffeine that are too numerous to list, as well as prescription and non-prescription drugs that contain caffeine.

Chemical Composition

Caffeine is 1,3,7-trimethylxanthine, a methylxanthine closely related to theophylline, aminophylline and theobromine (chocolate).

Mechanism of Action

Caffeine is a stimulant that acts through a number of pathways. Although early research focused on elevated plasma epinephrine and free fatty acids as the glycogen sparing mechanism behind endurance performance improvements, more recent studies have cast doubts upon this theory. The similarity of caffeine to important endogenous purines, such as adenine, guanine, hypoxanthine and uric acid, probably defines the mechanisms of action, of which adenosine receptor antagonism appears to be the most relevant (1). Caffeine's well-documented effects, including increased mental awareness, metabolic rate and lipolysis, enhanced skeletal and cardiac muscle contractility, and decreased perception of fatigue, appear to be mediated through a combination of direct effects of caffeine, effects mediated by its metabolites, such as paraxanthine and theophylline, or via indirect effects through stimulation of catecholamine release and neurotransmitter function, such as dopamine or norepinephrine (2,3). Direct effects on sodium-potassium pump activity, increased cyclic-AMP, and increased permeability of the sarcoplasmic reticulum to Ca^{++} contribute to the increased contractility of skeletal and cardiac muscle (1). Indirect effects from catecholamine release as well as the direct effect on cyclic-AMP lead to stimulation of lipolysis (3). Caffeine stimulates the central nervous system (CNS) by adenosine

receptor antagonism, which removes the negative modulatory effects of adenosine from dopamine receptors to stimulate dopaminergic activity and inhibit arginase activity. Inhibition of arginase activity makes more arginine available for other metabolic pathways in the brain, including production of NO and agmatine, a neurotransmitter involved in pain modulation (4).

Reported Uses

Caffeine is commonly used to increase energy levels, combat drowsiness, relieve nasal and bronchial congestion, promote weight loss, increase metabolic rate and improve athletic performance. Its stimulatory effects are used to increase mental alertness, improve cognitive performance, and reduce mental or physical fatigue. Caffeine has been taken as an aphrodisiac. In combination with ephedra, caffeine is used as a euphoriant, instead of illicit amphetamines.

Caffeine has a number of acceptable medical uses: as an adjunct in pain management, a treatment for neonatal apnea and acute respiratory depression, a diuretic, and as a seizure extender in electroconvulsive therapy. It may also be used to increase blood pressure in hypotension or cardiac insufficiency and in the treatment of depressive states, particularly when associated with generalized muscle weakness.

Less-accepted “alternative” uses of caffeine or its herbal or botanical sources include treatment or prevention of a diverse assortment of ailments across every organ system and as a tonic or general remedy. Coffee enemas have been used to treat various forms of cancer.

Dosages

Performance improvements begin to be detectable at intakes as low as 3 mg/kg. The optimal ergogenic dose appears to be around 5-6 mg/kg, equivalent to about 3 or 4 cups of brewed coffee. It is usually taken an hour prior to exercise. Doses above this fail to demonstrate any further performance improvements, but do increase the risk of associated side effects (5).

Scientific Evidence

Whereas many questions remain about caffeine’s mechanisms of action, its physiologic and psychological effects are well documented. It improves mental performance following prolonged sleep deprivation, potentiates pain relief, and may be effective, with or without ephedra, for weight loss (1,5). Multiple studies have demonstrated performance improvements across a wide range of endurance events. The studies consistently report decreased fatigue, measured as increased time to exhaustion, may be due to glycogen-sparing or an altered perception of fatigue and effort (1,2,6,7). Recent studies have also shown performance benefits in shorter duration events, particularly with a burst in the last few minutes after prolonged exercise (5). Whereas sprint and power increases are less consistently reported, at least one study reported a 7% power improvement, probably explained by caffeine’s effects on skeletal muscle contractility. It also appears that caffeine’s effects are more profound or more easily measured in trained rather than untrained or recreational athletes. This may be due to the greater interperson variability in the performance of participants who are untrained. There is also considerable variation among individual responses to any given dose of caffeine. Some “non-responders” may experience minimal ergogenic benefits from caffeine while at the same time notice adverse effects at much lower doses. Ergogenic benefits can be seen at relatively low doses (1-3 mg/kg), and at least one study actually reported decreased performance benefits at 9 mg/kg. There is no evidence of a dose-response relationship (5). Thus, while the potential for abuse and misuse exists, caffeine appears ergogenic for well-trained athletes across a broad spectrum of sporting events and relatively safe at the moderately low doses at which these benefits are seen.

Adverse Reactions

CNS: Insomnia, nervousness, restlessness, tremors, delirium, convulsions, headache, agitation, hyperesthesia, tinnitus, mania, tolerance, habituation, psychological dependence, fatigue

CV: Tachycardia, palpitations, premature ventricular contractions, other arrhythmias

GI: Gastric irritation, abdominal spasms, cramps or bloating, nausea, vomiting, liver dysfunction, borborygmi, flatus, increased stomach acid, ulcers, increased risk of H. pylori infection, constipation

GU: Diuresis, painful urination, increased excretion of calcium and magnesium;

Musculoskeletal: Rhabdomyolysis

Other: Allergic reaction, muscle spasm, increased intraocular pressure, elevated blood sugar, elevated cholesterol, increased homocysteine levels, bleeding diathesis. Coffee enemas can cause severe electrolyte abnormalities and sometimes septicemia leading to severe side effects including three reported deaths.

Drug Interactions

- Psychoactive drugs: The stimulatory effects of caffeine may increase or decrease the effectiveness of a wide variety of psychoactive drugs and/or increase the likelihood of side effects.
- Drugs metabolized by cytochrome p450: Caffeine is metabolized by this common pathway and may compete for elimination with many common medications, alcohol and grapefruit juice.
- Drugs with additive effects: These include α -adrenergic agonists, ephedrine and phenylpropanolamine.
- Monoamine Oxidase Inhibitors (MAOIs): Caffeine could precipitate a hypertensive crisis.
- Acid inhibiting drugs: Caffeine might interfere with these by increasing stomach acid.
- Analgesics: Caffeine general potentiates pain relief.
- Diabetic drugs: Caffeine has been reported to increase and decrease blood sugars.
- Anticoagulant and anti-platelet drugs: Caffeine may have antipathetic and even fibrinolytic activity.
- Alendronate (Fosamax): Caffeine may decrease the absorption of alendronate.
- Ergotamine: Caffeine may increase the absorption of ergotamine.
- Lithium: Caffeine withdrawal reportedly increases lithium levels, worsening the associated tremor.
- Creatine: Caffeine may interfere with the ergogenic effects of creatine.

Contraindications

Caffeine could aggravate anxiety disorders, depression, bleeding disorders, peptic ulcer disease, and glaucoma. People with heart disease should avoid caffeine due to its effects on homocysteine and cholesterol levels and the increased propensity for cardiac arrhythmias. Caffeine's variable effects on blood glucose could interfere with blood glucose control in those with diabetes. Its diuretic effects may aggravate some kidney disease and its effect on urinary

calcium excretion could aggravate osteoporosis. Caffeine may increase blood pressure in hypertensive patients unless they are already habituated. Cocoa may aggravate irritable bowel syndrome and, by reducing lower esophageal sphincter pressure, gastroesophageal reflux disease (GERD). Cocoa may also trigger migraine headache in certain individuals (3).

Comments

Caffeine is the most widely used pharmacologic substance. American society has a history of adding addictive substances to food and drink in order to sell more, as was the motivation behind cocaine in the original Coca-Cola formula. Since cocaine can no longer be used as a food or drink additive, caffeine has become a common substitute, particularly in soft drinks (2). Overuse is associated with a number of serious adverse events (8,9,10). Specifically, several reports in the literature indicate that excessive ingestion of caffeine can lead to rhabdomyolysis (13,14). Finally, caffeine used in combination with other products can negate benefits from those products, such as creatine (11).

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2. Ginseng

Sources

Ginseng refers to extracts derived from the plant family Araliaceae. The most common members of this family are listed below, along with other common names by which each is called.

- *Panax ginseng* (or *P. shinseng*) includes Asian or Asiatic, Chinese, Korean, and Oriental ginseng. It may also be referred to as guigai, jintsam, ninjin, radix ginseng rubra, ren shen, sang, or seng;

- *Panax quinquefolius* includes Canadian, North American, Ontario, and Wisconsin ginseng, also called Anchi, red berry, five-leafed ginseng, five-fingers root, garantogen, jen-shen, and ninsin;.
- *Eleutherococcus* (or *Acanthopanax*) *senticosus* or *Hedera senticosa* includes Siberian, Russian, and Eleuthero ginseng, Ussurian thorny pepperbush, touch-me-not, ci wu jia, devil's shrub or bush, shigoka, Thorny Beaver of Free Berries, Untouchable, Ussuri, wild pepper, and Taiga root;
- Red and white ginseng both refer to *Panax ginseng*, but red ginseng is steamed and dried in heat or sunlight while white ginseng is simply the dried or powdered root.

Other true ginseng not as well studied include:

- *Panax japonica* is Japanese ginseng or zhu je, a closely related species with different properties;
- *Panax notoginseng* (or *P. pseudoginseng*) includes tienqi ginseng, field seven, pseudoginseng root, samch'il, san qi (or qui), sanshichi, three seven, or tian qi
- *Panax trifolius* is Dwarf ginseng. Also known as ground nut, it grows primarily in wooded areas of the northeastern United States and Canada
- *Panax zingiberensis*, commonly called ginger ginseng, is an endangered species in China.

Please read product labels - hundreds of products contain Ginseng but you may not expect it to be in the product. Examples: Brain Fuel, Centrum Focused Formulas - Energy, EQ-10, Living Energy, Men's Support, PMS Forte, Power Thin, Revenge, Nicodrops, One-A-day Active Formula, Stress Action, Turbo Trim Plus and many others!

NOTE: A large number of botanicals are called by names that use the word ginseng. DO NOT CONFUSE them with true ginseng:

Table 1. Plants similarly named or similarly used that are NOT True Ginseng

Ayurvedic or Indian ginseng	Ashwagandha	<i>Withania somnifera</i>
Bastard or false ginseng or dangshen	Bellflower	<i>Codonopsis pilosula</i>
Bitter ginseng or kushen	Pagoda tree	<i>Sophora japonica</i>
Blue or yellow ginseng	Blue Cohosh	<i>Caulophyllum thalictroides</i>
Brazilian ginseng	Suma	<i>Pfaffia paniculata</i>
Cinnabar-colored ginseng or danshen	Red Sage	<i>Salvia miltiorrhiza</i>
Northern sand ginseng or beishashen	Beach Silvertop	<i>Glehnia littoralis</i>
Peruvian ginseng or ayak willku	Maca	<i>Lepidium peruvianum</i>
Prince's ginseng or taizishen	Lesser Ginseng	<i>Pseudostellaria heterophylla</i>
Purple ginseng or quan shen	Bistort or Dragonwort	<i>Polygonum bistorta</i>
Sand ginseng or nanshashen	Ladybells	<i>Adenophora triphylla</i>
Southern ginseng, xianxao or fairy herb	Jiaogulan	<i>Gynostemma pentaphyllum</i>

Table 1. Plants similarly named or similarly used that are NOT True Ginseng

Wild red desert or American ginseng	Ca aigre	Rumex hymenosepalus Torr
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Chemical Composition

Ginseng roots contain at least 30 positively identified saponin triterpenoid glycosides (4) referred to as ginsenosides, a term developed by Asian researchers. These same constituents were referred to as panaxosides by early Russian researchers. Eleutherosides are the analogous but distinct constituents of Siberian Ginseng (1). Exact proportions of these various constituents vary greatly based on species, growing conditions and preparation (1,2)

Other constituents include arabinose, calcium, camphor, iron, mucilage, resin, polysaccharide, glycans, peptides, maltol, flavonoids, volatile oil, and vitamins A, B₁₂, and E (3). Additionally, Siberian ginseng contains coumarins, lignans, and phenylpropanoids whereas Panax ginseng contains panaxans and Panax quinquefolius contains quinquefolans A, B, and C (2,4).

Mechanics of Action

The ginsenosides and eleutherosides, considered to be the active constituents in ginseng roots, have a wide range of pharmacological activity and in some cases, appear to counteract each other's activity. This is consistent with the classification of ginseng as an adaptogen, a term used for generally innocuous substances that have a wide-variety of effects and tend to modulate parameters toward normal (2). Increased NO production has been measured in multiple tissue types and could account for many of the clinical effects. Ginseng may affect stress through the hypothalamic-pituitary-adrenal (HPA) axis, and increased adrenocorticotropin and cortisol levels have been reported with ginseng use (1). Ginseng may enhance acetylcholine actions through an unknown mechanism, which could account for its reported memory improving effects (2).

Reported Uses

As implied by the name panax, or “all-healing,” ginseng has been touted for a broad range of ailments from AIDS to zoster (2,3,4,5,6). In traditional Chinese medicine, it is used to restore Qi, or life energy (6). Ginseng is often consumed as a tonic for vitality, health, longevity, strength, wisdom, and generalized well-being (1,2,7). Chinese herbalists recommend ginseng for the ill, weak, and elderly, and feel that it is “wasted on the young” (4). Ginseng is often taken to slow or decrease the effects of aging, and for such age-related conditions as hot flashes, diabetes, cancer and Alzheimer's disease (2,7). Still, athletes may take ginseng to improve physical and athletic stamina or as herbal support during rigorous training; they may take Siberian ginseng to increase work capacity (7,8,9).

Dosages

Generally dosing is around 0.6 to 3 grams of root powder 1 to 3 times per day for Panax ginseng, and as a capsule or extract standardized to 4-8% ginsenosides, 200–600 mg/day. Dosing is slightly lower for P. quinquefolius and E. senticosus. Sometimes ginseng is taken continuously, but cycling is usually recommended. Ginseng is taken for 3 weeks to 3 months followed by 2 weeks to 2 months off.

Scientific Evidence

Ginseng preparations have antioxidant properties similar to vitamins A, C and E. Several studies show increased immune system activity, particularly that of T-cells and lymphocytes integral to the body's defense against cancer and AIDS. Improvements in a number

of mental tasks, mood, memory, and reaction time have been shown. In animals, ginseng facilitates insulin release and increases peripheral insulin receptors (4). Research on ergogenic effects is inconsistent and fraught with experimental design flaws, including inadequate numbers or lack of double blind, control and placebo protocols. Early Soviet research on Siberian ginseng involved thousands of subjects, including divers and cosmonauts, making E. senticosus one of the only dietary supplements studied in divers. Though the data are almost inaccessible and the experimental designs suspect, these studies showed improvements in work output, muscle strength, resistance to fatigue and recovery from exercise (7,8). Many animal studies showed improvements in exercise performance, but large parenteral doses of ginseng or ginsenosides were used, despite known biotransformation in the gastrointestinal tract. Still, dose-response and duration effects are evident, and the longer duration studies with higher doses and larger numbers of subjects were more likely to show an ergogenic benefit. Two recent double blind studies of athletes were unable to demonstrate any ergogenic effect of Siberian ginseng (9,10). Furthermore, the observed benefits may be more profound in recreational athletes over 40 years old (1).

Adverse Reactions

CNS: insomnia, vertigo, headache, euphoria, mania

CV: tachycardia, palpitations, hypertension, hypotension, edema

GI: decreased appetite, diarrhea, cholestatic hepatitis

Endocrine: estrogen-like effects such as post-menopausal vaginal bleeding, mastalgia, amenorrhea and gynecomastia

Skin: pruritis, allergic skin reaction, Stevens-Johnson syndrome

Miscellaneous: hyperpyrexia, cerebral arteritis, neonatal death

Most side effects are mild and reversible when they occur. Causal relationships often cannot be established in combination products that contain ginseng as one of many ingredients. Ginseng preparations have been found adulterated with stimulant drugs such as ephedrine and pseudoephedrine, which may effect adverse reactions or drug interactions (11).

Drug Interactions

- Caffeine: Large doses of ginseng taken with caffeine may cause hypertension.
- Vitamin C: Vitamin C can interfere with the absorption of ginseng.
- Morphine: Ginseng may block the pain relieving effects of opioid analgesics.
- Immunosuppressants: The immune-stimulating effects of ginseng may interfere with these drugs.
- MAOIs: Interaction may cause insomnia, headache, tremor, or hypomania.
- Stimulants: Ginseng may potentiate these effects.
- Sedatives, including alcohol and barbiturates: Sedative effects of Siberian ginseng may be additive.
- Kanamycin: Siberian ginseng may improve the effectiveness of this antibiotic.
- Anti-diabetic drugs, including insulin: These may be affected by the hypoglycemic effects of ginseng.
- Anticoagulant/Antipathetic drugs: Theoretically there could be an increased chance of bleeding.
- Warfarin: Ginseng might decrease the effectiveness.

- Drugs metabolized by cytochrome P450: Ginseng may have a slight, probably subclinical, effect.

Contraindications

Chinese herbalists do not recommend the use of *P. ginseng* for those with disorders such as ulcers, hypertension, tension headache, nervousness, mental imbalance, inflammation, and fever. Modern Western medicine concurs with these, and recognizes the potential for ginseng to aggravate any of these conditions, including insomnia and agitation in schizophrenia. Pregnant women should not use, due to unknown safety considerations. Also, persons with diabetes should not use ginseng due to its unpredictable effects on blood glucose. Lastly, persons with hormone sensitive cancers should not use due to its potential estrogenic effects.

Comments

Ginseng is the most studied herb for human physical performance (1). It was the second best selling herbal supplement in the United States in 2000 with gross retail sales of \$62 million (7).

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3. Polylactate

Sources

Cytomax, Gulp n'Go, MusclEnergy, Metabolol II

Chemical Composition

Polylactate is a semi-soluble, non-acidic mixture of mostly organic amino acid salts with a small amount of inorganic salts of lactate.

Mechanics of Action

The body needs and uses lactate. During strenuous exercise, circulating lactate becomes the predominant energy source for heart muscle. Lactate is also a substrate for glucose formation. By supplying additional carbohydrate (CHO) energy sources, polylactate may improve athletic performance by sparing glycogen stores (1,2). Additionally, polylactate provides non-acidic lactate salts, which may buffer lactic acid production during exercise and reduce the "burn."

Reported Uses

Polylactate is used in sports drinks to delay the onset of fatigue, improve performance, and speed recovery (2)

Dosages

Poly lactate is generally taken as a 7% solution in water or glucose polymer, 5 minutes prior to exercise and at 20 – 30 minutes intervals throughout. Although this beverage is generally taken ad libitum, at least one study used a standard of 0.3 g carbohydrate/kg body weight (2).

Scientific Evidence

No ergogenic effects have been demonstrated in any reputable studies of poly lactate alone or in combination with a glucose polymer (4,5). One study demonstrated higher blood pH and bicarbonate levels after exercise in poly lactate-supplemented individuals as compared to those given a glucose polymer solution (3).

Adverse Reactions

GI: Beverages with up to 0.75% poly lactate are tolerated well. Above this there is an increase in the incidence of severe gastrointestinal problems (5).

Drug Interactions

None reported

Contraindications

None reported

Comments

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4. Inosine

Sources

Inosine is most commonly found in supplements that claim to be “energy promoters”. Naturally, inosine is found in brewer’s yeast and organ meats, but it is also available as a supplement (1,2).

Whereas inosine can be found alone without other agents, it is also found in a number of other products, such as Weight Gainer 2200 Gold, and Pro Performance.

Chemical Composition

Inosine’s scientific names include 2,3-Diphosphoglycerate; 6,9-Dihydro-9-B-D-ribofuranosyl-1H-purin-6-one; and 9-B-D-ribofuranosylhypoxanthine.

Mechanism of Action

Inosine is a nucleoside and a precursor to adenosine and to uric acid, a compound that occurs naturally in the body. Uric acid is believed to block the effect of a toxic free-radical compound (peroxynitrite). Inosine is also involved in the formation of purines and may play a role in energy metabolism (1,2).

It has been postulated that inosine might enhance 2,3 DPG levels in red blood cells. Higher 2,3 DPG levels should be associated with a more rapid release of oxygen from blood cells to tissues and theoretically enhance energy production by increasing ATP (1,2). However, inosine supplementation over a short period of time (10 days) was not shown to increase levels of 2,3 DPG (3).

Reported Uses

Inosine is used mainly to enhance athletic performance. The claims include increased energy levels, improved endurance performance, enhanced ATP production, increased oxygen delivery, and reduced lactic acid accumulation. However, it is also being used by persons with multiple sclerosis to raise uric acid levels.

Dosages

A common amount of inosine taken by athletes is 5 to 6 grams per day in studies looking at the effects of supplementation on athletic performance (1). A dose of 3 grams/day has been used with multiple sclerosis (4).

Scientific Evidence

Most of the literature for inosine has focused on its effects as an ergogenic aid (3-5). Controlled studies have concluded that inosine does not improve athletic performance and may even impair it (3-5). However, other literature has focused on other uses. Patients with MS were treated with inosine in amounts up to 3 grams per day for 46 weeks and three of the ten treated patients showed some evidence of improved function and the others remained stable (6). Controlled studies are needed to confirm these preliminary results.

In a slightly different arena, some preliminary research suggests that inosine may stimulate axon growth from uninjured nerve cells to injured nerve cells in the CNS (7). Whether or not this could restore function in humans after spinal cord injuries is an active area of research.

Adverse Reactions

No adverse reactions or side effects have been reported with the use of inosine for two to five days in the limited research available. However, unused inosine is converted by the body to uric acid, so that inosine should not be used in persons who have gout (1).

Drug Interactions

- Probenecid, Allopurinol: Although no direct drug interactions have been noted, inosine should not be used with these drugs because it may make gout worse.

Contraindications

Inosine should not be used in persons who have gout (1). In addition, pregnant or lactating should avoid using inosine because insufficient information is available.

Comments

There is insufficient information about the effects and safety of inosine. Further research needs to be done to examine any benefits or detriments that could occur from supplementation.

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5. Coenzyme Q₁₀

Sources

Coenzyme Q₁₀ (CoQ₁₀) is found naturally in fish and meats, as it is part of the mitochondria of skeletal and cardiac muscle cells, kidneys, pancreas, heart, and liver (1). Artificially, CoQ₁₀ is manufactured by fermenting beets and sugar cane along with special strains of yeast (2). It can be purchased in supplement form and is usually marketed as CoQ₁₀. However, it can also be purchased in other commercial products under names such as “Pro Performance”.

Chemical Composition

CoQ₁₀, also known as Q₁₀, vitamin Q₁₀, ubiquinone, or ubidecarenone is a compound. The Q and the 10 in coenzyme Q₁₀, refer to parts of the compound’s chemical structure. Scientific names include Ubiquinone, Ubidecarenone, and Mitoquinone.

Mechanism of Action

CoQ₁₀ is used by cells as a crucial component of the oxidative phosphorylation process in mitochondria where the energy in CHO’s and fatty acids is converted into ATP to produce energy needed for cell growth and maintenance. Its importance in energy metabolism is the rationale for promoting CoQ₁₀ supplementation for athletic performance. Moreover, evidence that supplementation with CoQ₁₀ increases tissue and mitochondrial CoQ₁₀ levels and enhances ATP production has been provided.

CoQ₁₀ is also used by the body as an antioxidant (3). CoQ₁₀ appears to be able to delay or prevent the oxidation of membrane-bound lipid peroxide free radicals, and for this reason it has been used to help prevent atherosclerosis and heart disease (3,4). CoQ₁₀ levels are often low in people with certain diseases and supplementation has been shown to be effective in people with such diseases, including congestive heart failure, hypertension, periodontal disease, certain muscular diseases, and AIDS (1).

Reported Uses

CoQ₁₀ is used orally for treating congestive heart failure, angina, diabetes, hypertension, periodontal disease, and breast cancer (1,2). It is also used for treating Huntington’s disease, Parkinson’s disease, muscular dystrophy, reducing chronic fatigue symptoms, and boosting the immune system in HIV/AIDS patients (1). CoQ₁₀ is also taken to increase aerobic capacity for improved exercise performance, but evidence to support its effectiveness is lacking. CoQ₁₀ is also used topically to treat periodontal disease (1).

Dosages

The recommended dosage is 50 - 100 mg/day for any treatment (1). However, 100-200 mg split up into three doses per day has been taken without any adverse side effects for treatment of heart failure, angina, hypertension, diabetes, and AIDS (3), and up to 1,200 mg per

day has been used for Parkinson's disease (1). Most doctors recommend that CoQ₁₀ be taken with meals to improve absorption.

Anecdotal reports suggest large amounts of CoQ₁₀ may improve the outcome of certain types of cancer. However, controlled trials are needed to confirm these preliminary observations and people with cancer should not take additional CoQ₁₀ without discussing it with their physicians.

Scientific Evidence

Although products containing CoQ₁₀ are being marketed to endurance athletes, research is conflicting (6). A recent article systematically reviewed the effects of CoQ₁₀ on physical performance and noted 11 studies: six showed a positive effect in terms of increasing maximal aerobic capacity whereas the other five demonstrated no significant effects. Of note is that five of the six positive studies were not published in peer-reviewed journals whereas the negative ones were. Another positive aspect of the studies was that trained and untrained athletes were studied, and CoQ₁₀ was given for in doses ranging from 90 to 100 mg per day for a period of four to eight weeks. Thus, it would seem critical that additional work be carried out before a determination is made, but it does appear that a slight improvement in exercise capacity may result from supplementation with CoQ₁₀.

Another realm of research has focused on using CoQ₁₀ to prevent or treat a number of diseases, and many of these studies have shown CoQ₁₀ supplementation to be beneficial, particularly with respect to hypertension, heart disease and cancer (1,6). Again, in a review of eight studies relating to hypertension and CoQ₁₀, supplementation with CoQ₁₀ (100 to 200 mg/day) resulted in significant decreases in both systolic and diastolic pressure (6). CoQ₁₀ may also be of benefit in heart failure. Rosenfeldt et al. (6) performed a randomized, double blind, placebo-controlled pilot study wherein patients in heart failure received either placebo or 150 mg of CoQ₁₀ daily for three months. At the end of the three months the persons in the CoQ₁₀ group showed improvement in exercise tolerance and clinical indicators of heart failure (6). Thus, this may be another area for additional research. Finally, a number of studies have focused on using CoQ₁₀ as an adjuvant therapy for patients undergoing conventional cancer treatments, primarily cancers of the breast, lung, prostate, pancreas, colon, kidney, and head and neck (5). One rationale for a beneficial effect is the ability of CoQ₁₀ to stimulate the immune system and increase resistance to disease. In summary, the story of CoQ₁₀ is unfinished and may be one of the more promising agents.

Adverse Reactions

GI: Heartburn, nausea, diarrhea, and appetite suppression (1,3).

Consuming a meal and splitting up doses throughout the day usually prevents these side effects (3).

Drug Interactions

All information regarding interactions is derived from reference (1)

- Antihypertensives: May affect blood pressure with additional effects with medication used for hypertension.
- Beta-Blockers: Some beta blockers (Inderal, Metoprolol) inhibit CoQ₁₀-dependent enzymes in the myocardium. Taking CoQ₁₀ supplements may reduce this adverse effect of beta-blockers.

- **Chemotherapeutic Agents:** The effects of CoQ₁₀ on cancer patients are not entirely known. Supplementation may protect tumor cells from chemotherapeutic agents and should be avoided without advice from a physician.
- **Hypoglycemic Agents:** Oral hypoglycemic agents may inhibit the activity of CoQ₁₀ dependent enzymes. The effects of CoQ₁₀ supplementation on glycemia are still unknown.
- **Insulin:** Although most evidence shows otherwise, there is some concern that CoQ₁₀ may decrease blood glucose and insulin requirements in patients with diabetes.
- **Warfarin:** CoQ₁₀ may have pro-coagulant effects and can decrease the anticoagulation effects of Warfarin if taken in high doses.

Contraindications

It is recommended that women who are pregnant or lactating avoid using CoQ₁₀ because insufficient information is available on that topic.

Comments

CoQ₁₀, first identified in 1957, is widely used in Japan, Europe, and Russia. Most of the CoQ₁₀ used in the US is supplied by Japanese companies. Cigarette smoking depletes the body's store of CoQ₁₀ (1).

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6. Bee Pollen and Royal Jelly

Sources

Bee pollen refers to the pollen on the legs and bodies of worker honeybees (*Apis mellifera*) collected by the bees from the flowers of many species of plants. Bee pollen, which comes from various plants, including buckwheat, maize, pine, rape, timothy grass, corn, and rye, is available commercially in capsules, tablets, granules, liquid extracts, tinctures, creams, and salves. Some popular products include Natrol Thera Zinc Lozenges-Menthol, Puritan's Pride Time Release Athletes Formula, and Futurebiotics Living Energy (1,2).

Royal jelly, also called honeybee milk or bee spit, is a milky secretion produced by glands in the heads of nurse honeybees. This milk is used to feed larvae during the first three days of life and thereafter fed only to the puerile queen. Royal jelly can be found as ampules, capsules, tablets, cream, extract, liquid, lotion, ointment, powder, soap, and even toothpaste. Some products include Jamieson Red Dragon Imperial Royal Jelly, Denman Scientific Research ZymaX A.M. Formula, and The Vitamin Shoppe Super Energy Up (1,3).

DO NOT CONFUSE either of these with bee venom, propolis (bee gum), a resinous material from poplar and conifer buds that bees use to maintain their hives, or honey.

Chemical Composition

Bee pollen is composed of CHO (55%), protein (35%), minerals and vitamins (3%), fatty acids (2%), and other substances (5%). Geographic location and plant source of the pollen can cause significant variability in the vitamin and mineral content of the products. Phytic acid, a natural plant antioxidant, is also found in high concentration in bee pollen. Besides these chemical constituents, at least 15 other key compounds have been identified in bee pollen, including the phenol flavonoids rutin and quercetin, but the shells of individual grains of pollen are not readily digestible such that only a small percentage of nutrients may actually be processed.

Royal jelly typically contains about 60% to 70% water, 12% to 15% crude proteins, 10% to 16% sugar, 3% to 6% lipids, and 2% to 3% low molecular weight compounds, such as vitamins, salts, and free amino acids. As with bee pollen, the proportions vary based on geographic area and climatic conditions (1).

Mechanism of Action

The energy claims for bee pollen are based on the assumption that its constituents provide the optimum combination of various vitamins and minerals involved in energy metabolism. Its popularity is based mostly on anecdotal reports.

Royal jelly has a similar nutritional profile, but additionally, as the food that sets worker bees apart from the queen bee, royal jelly is thought to promote longevity and vitality (3).

Reported Uses

Bee pollen is used to increase energy during exercise and promote faster recovery. It is touted as being able to prolong endurance, promote weight loss, and stimulate the immune system, but it may also be taken as an appetite stimulant. It has been used for bleeding and gastrointestinal problems, for alcohol intoxication, and as a general tonic (4). Topically bee pollen is used to treat eczema and other skin conditions (1).

Athletes use royal jelly to combat fatigue, slow the effects of aging, and boost the immune system. Royal jelly is also used for bronchial asthma, allergic rhinitis, insomnia, pancreatitis, bone fractures, hyperlipidemia, and liver and kidney diseases. It is used to treat “failure-to-thrive” in newborns and topically as a skin tonic and hair growth stimulant (1,3).

The phytic acid in bee pollen may be useful in lowering the incidence of colon cancer and protecting against other inflammatory bowel diseases (2).

Dosages

Typical dosing for bee pollen ranges from 250 mg to 3 g/day.

Royal jelly dosages range from 50 mg to 2000 mg, although 50-100 mg/day has been shown to be efficacious for hyperlipidemia.

Scientific Evidence

Several studies of bee pollen use in athletes in the 1970 and 80's showed no significant differences in various measures of performance and laboratory values when compared with placebo (5,6,7). However, one double blind, placebo-controlled study of 20 swimmers over 6 weeks in 1982 revealed a statistically significantly fewer training days missed due to upper respiratory infections in the bee pollen (4 versus 27) as compared to the placebo group (8).

Only one scientific study on anything other than safety issues is available regarding the effects of royal jelly in humans. A 1995 review paper, which included a number of unpublished studies, concluded that 50 - 100 mg/day of royal jelly in humans with hyperlipidemia

averaged a 10% reduction in total serum lipids and a 14% reduction in cholesterol (9). Otherwise, minimal scientific evidence for a beneficial effect of royal jelly can be found.

Adverse Reactions

Bee pollen tends to be fairly innocuous with little or no risk of consuming toxic levels of any one specific nutrient.

CNS: Decreased memory, headache

GI: Nausea, abdominal pain, diarrhea

Skin: Pruritis, conjunctivitis, urticaria

Other: Anaphylaxis (10), rhinitis, bronchospasm, acute hepatitis, hyper-eosinophilia

Royal jelly appears to cause few side effects in non-allergic people, but people with a history of atopy or asthma appear to have a high rate of allergic symptoms similar to those with bee pollen.

CNS: Decreased memory, headache

GI: Hemorrhagic colitis (11)

Skin: Eczema

Other: Facial edema, dyspnea, status asthmaticus and death

Drug Interactions

No drug interactions have been described or reported for bee pollen or royal jelly.

Contraindications

Bee pollen is contraindicated in those with pollen allergies or hypersensitivity and, because of the reported cases of hepatitis, in those with existing liver disease (1). Those with asthma or atopy should avoid royal jelly (1). Anyone allergic to bee stings, honey, or other bee products should use caution with bee pollen or royal jelly (2-4,8).

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7. Ribose

Sources

Ribose, also known as D-ribose or D-ribofuranose, is the naturally occurring sugar moiety of ATP. Supplement products with D-ribose include Muscle-Link Ribose, Universal Ribose, EAS Riboforce, PBL Liquid Ribose, Pinnacle Adrenerlin, Trans X, Myomax Champion Nutrition's Revenge, Bodyonics, Ltd.'s Adrenerlin and Pinnacle CreaRibose ATP Kichers, and Jarrow Formulas' Buffered TLC (1).

Chemical Composition

D-ribose is a 5-carbon monosaccharide, or an aldopentose found as a structural component of many chemicals in the body, including ATP, ADP, and AMP. It is a key component in both *de novo* nucleotide synthesis and salvage pathways. Most of the body's ribose is synthesized endogenously through the pentose phosphate pathway.

Mechanics of Action

Ribose is the rate-limiting substrate in the production of phosphoribosyl-pyrophosphate (PRPP), a precursor for the salvage and *de novo* synthesis of adenine nucleotides needed to regenerate ATP. Animal studies suggest that exogenous ribose with adenine improves myocardial ATP recovery (1,2). Manufacturers have suggested that oral supplementation of ribose can increase anaerobic performance because of its potential to improve skeletal muscle energy and nucleotide balance (3).

Reported Uses

Ribose is marketed as a stand-alone dietary supplement or as part of a multiple supplement product. The main market claims are increased energy, increased muscle function, quicker recovery times, enhanced effectiveness of creatine, and improved cardiac function. These claims are based on the theory that ribose maximizes ATP stores and increases the rate of ATP regeneration (1,2). Ribose has been used to improve exercise tolerance in patients with McArdle's disease, but with mixed results (3,4).

In addition, ribose has been used intravenously to facilitate removal of thallium-201 from healthy non-ischemic cardiac tissue, leaving it only in ischemic tissue. This allows for better definition of ischemic myocardium during treadmill testing (1,5). Ribose has been used orally to prevent symptoms such as cramping, leg pain, and stiffness after exercise in patients with myoadenylate deaminase deficiency (MAD) (1).

Dosages

Oral: Generally 2-6 grams 30 minutes prior to exercise or at bedtime on non-exercise days are recommended. To improve exercise tolerance in patients with coronary artery disease, a dose of 15 grams four times per day has been used. Patients with MAD can take 3 grams every 10 minutes starting one hour before exercise and continuing until the exercise session is complete.

Intravenous: For coronary artery imaging, 3.3 mg/kg/minute of a 10% ribose solution every 30 minutes has been used.

Scientific Evidence

From a theoretical and mathematical perspective, supplemental ribose has the potential to increase the rate of adenosine production and ATP synthesis by approximately 3-4 fold, such that recovery of ATP stores after intensive training could be reduced from 1-4 days to 6-24 hours (4). Multiple studies to date have tested the hypothesis that ribose supplementation decreases ATP regeneration time and results in quicker recovery times and better performance

after and during intense exercise (6-9). Most studies have shown no improvement in athletic performance or in recovery times after intense exercise. For example, oral ribose supplementation with 4 g doses four times a day for six days did not beneficially impact postexercise muscle ATP recovery or maximal intermittent exercise performance in healthy males (6). However, in a recent study by Hellsten et al. (7), participants received either ribose (200 mg/kg body wt) or placebo three times per day for three days and underwent an intensive training session at the end of each treatment. They found that oral intake of ribose after training enhanced the rate of adenine nucleotide resynthesis as compared to placebo. Differences in methodologies, dosing and other factors may explain the discrepancies, and more research will be needed to determine the role of ribose in performance enhancement. Still another randomized, placebo-controlled trial demonstrated no consistent benefit of ribose in former competitive athletes (8). Ribose supplementation led to increases in mean power and peak power only in four of six sprints, but significance was noted only for sprint 2. They concluded that supplementation with ribose results in small and inconsistent benefits (8). Similarly, Kreider et al. (9) found that Results indicate that oral ribose supplementation (10 g/d for 5 d) had no affect on anaerobic exercise capacity or metabolic markers in trained subjects.

Interestingly, abundant and sound scientific evidence exists for the use of ribose in cardiac ischemia (2,4,10). Supplemental ribose allowed subjects with coronary artery disease to exercise for significantly longer as compared to without ribose and longer than subjects who consumed a placebo supplement (4). Pliml et al. (10) showed that administration of ribose by mouth for 3 days in patients with CAD improved the heart's tolerance to ischemia. The presumed effects on cardiac energy metabolism offer new possibilities for adjunctive medical treatment of myocardial ischemia.

Adverse Reactions

CNS: Headache

GI: Diarrhea, gastrointestinal discomfort, nausea, slightly increased insulin;

Miscellaneous: Decreased blood glucose levels, decreased phosphate levels;

Ribose supplementation is generally well tolerated, and no adverse effects have been reported in published studies. Since ribose is found in all cells of the body, it is generally recognized as non-toxic.

Drug Interactions

- Insulin: Ribose may increase the hypoglycemic effect of insulin and should be avoided by people taking insulin (1).
- Oral anti-hyperglycemic agents: Ribose may increase the hypoglycemic effect of oral anti-hyperglycemic agents such as the sulfonylureas, biguanides, alfa-glucosidase inhibitors, thiazolidinediones, and meglitinides (1).
- MAOIs: Ribose may enhance the hypoglycemic effects of MAOIs (1).
- Salicylates: Ribose may enhance the hypoglycemic effects of salicylates (1).

Contraindications

Theoretically, ribose should be avoided in patients with diabetes since it may interfere and enhance the glucose lowering effects of insulin or any oral anti-hyperglycemic agents. Similarly, ribose should be avoided in patients who have hypoglycemia, or diseases or conditions that may increase their risk for hypoglycemia (1).

Comments

Ribose supplementation is expensive. At a recommended price of \$70 for 100 g supply, a daily dose of 10-20 grams of ribose would cost \$50-100 per week (5). Therefore, with the current high-price tag of oral ribose supplements, ribose does not appear to be a cost-effective supplement for athletes (3). Still, competitive athletes who may be training once or more per day could notice benefits such as increased power output and increased time to exhaustion with regular ribose supplementation (due to enhanced ATP resynthesis following exercise-induced depletion) (4).

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8. 2-Dimethyl-L-Aminoethanol /Dimethylaminoethanol (DMAE)

Sources

2-Dimethyl aminoethanol, abbreviated DMAE, is also known as deanol aceglumate, deanol acetamidobenzoate, dimethylethanolamine, and N,N-dimethyl-2-hydroxyethylamine. DMAE is a naturally occurring compound found in high levels in anchovies and sardines; small amounts are also naturally produced in the human brain. The most common form of the supplement is deanol bitartrate. Deanol, once marketed as the prescription drug, Deaner, was taken off the market in 1983 when the FDA required testing that would have cost more than the drug's sales could support (1). Supplement products with DMAE include Novus Research's Brain Lightning, Source Natural's Focus Child and MegaMind, and Pacific BioLogic's Cognicine. Please note that DMAE is found in MANY products.

Chemical Composition

DMAE is a chemical produced naturally in the human brain. It may be used in the conversion of choline to the neurotransmitter, acetylcholine. It can be synthetically created by removing a methyl group from a nitrogen in a choline molecule.

Mechanics of Action

DMAE is a precursor to choline and might enhance central acetylcholine formation (1). It crosses the blood-brain barrier more easily than choline, and upon entry into the brain, is converted easily to choline (2). This increased level of choline, in theory, should increase the brain's ability to make acetylcholine, a very important neurotransmitter involved in memory, learning, recall, and thought processes (2,3). DMAE also appears to inhibit the oxidation of choline to betaine, which is involved in homocysteine metabolism, and may inhibit other reactions of choline metabolism (1).

Reported Uses

As a prescription drug, deanol was approved by the FDA as "possibly effective" for certain learning problems, hyperactivity, and hyperkinetic behavior (2). It is touted now for enhancing memory and mood, boosting cognitive function, increasing intelligence and physical energy, improving athletic performance, preventing aging or liver spots, promoting sleep at night, improving red blood cell function, improving muscle reflexes, increasing oxygen efficiency, extending life span, and treating autism and attention deficit disorder (ADD). DMAE may be used in the treatment of Alzheimer's disease or senile dementia (3). DMAE may also be used in patients with tardive dyskinesia, a movement disorder that can occur after using certain antipsychotics for several weeks (2).

Dosages

People typically begin with 100 mg per day and gradually increase to 500 mg per day. Doses have ranged from 10mg up to 2000 mg per day in clinical studies (2, 3).

Scientific Evidence

Numerous trials investigating DMAE as a possible treatment for tardive dyskinesia have been mixed, but mostly negative. DMAE has similarly been shown to have no significant effect in the treatment of Alzheimer's disease, amnesic disorders, age-related cognitive impairment and Tourette's syndrome (1). At least one double blind, randomized, crossover study showed DMAE, when used orally in combination with ginseng, vitamins, and minerals in 50 healthy male sports teachers, to be effective in improving total workload and maximal oxygen consumption during exercise in men whose maximal aerobic capacities were below 60 ml/kg/min (5). Interestingly, the improvement was associated more with the ginseng than the DMAE, but because the supplement contained multiple agents, the one responsible for the improvement could not be determined.

Adverse Reactions

- CNS: headache, insomnia, lucid dreams, dyskinesia syndrome, drowsiness, confusion, overstimulation, depression, hypomania, increased schizophrenia symptoms
- CV: mild blood pressure elevation
- GI: constipation, cramps
- Skin: urticaria
- Musculoskeletal: muscle tension in the neck, jaw, legs, and others

Drug Interactions

- Anticholinergic drugs: Theoretically, DMAE use might decrease the effect of drugs with anticholinergic activity due to the potential cholinergic activity of deanol (2,3).

Contraindications

Pregnant women and nursing mothers should avoid deanol (1,2). Because of its reported effects on betaine metabolism, those with elevated homocysteine levels should avoid DMAE (1). DMAE can worsen schizophrenia symptoms and may worsen depression. Avoid use in those with mood disorders (2,3). It is contraindicated in people with clonic-tonic seizure disorders (3).

Comments

Deanol has not been approved as a food additive in the US, nor is it an orphan drug, as some supplement advertising suggests. After finding it too expensive to be used in clinical trials for approval as a drug, it was repackaged as a nutritional supplement, because it occurs naturally in fish.

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B. Fat Burners/Lean Body Enhancers/Thermogenics/Weight Loss

1. Ephedra/Ephedrine

Sources:

Ma Huang, Metabolite, Xenedrine, Hydroxycut, Up Your Gas, Stackers, Thermagen, Ripped Fuel, and various teas (Mormon tea, Squaw tea, Teamster's tea). For a full listing of products containing ephedra, go to http://www.phentermine-info.org/hdp/hdp_products_ephedra.shtml.

Chemical Composition:

Ephedra is an evergreen plant found in various parts of the world, but most abundantly in the Far East. The active form of ephedra is the alkaloid, ephedrine, which is derived from the dried stem of one of three ephedra species. The ephedra plant also contains methylephedrine, pseudoephedrine, norephedrine, and ephedroxane.

Mechanisms of Action

Ephedrine, a sympathomimetic alkaloid, with α - and β -receptor agonist properties, has been shown to produce amphetamine-like effects. This compound acts as a CNS stimulant and produces mydriasis, enhanced myocardial contractility, increased heart rate,

bronchodilation, and peripheral vasoconstriction with a concomitant increase in blood pressure (1). The use of ephedrine has also been associated with various psychological events.

Reported Uses

Ephedrine products have been marketed in the United States for weight loss, increased energy, enhanced athletic performance, and mental alertness, but in January 2004 this product was banned by the Food and Drug Administration (FDA). Chinese medicine originally used ephedra to treat arthralgia, bronchial asthma, colds, edema, flu, headaches, and nasal congestion. In the US, many over-the-counter flu and sinus symptom relief products contain ephedrine or pseudoephedrine because of the well-documented vasoconstrictive effects on congested membranes.

Dosage

Prior to the FDA ban, the recommendation was that individuals using ephedrine limit the dose to 8 mg every 8 hours and the maximum dose to 24mg/day. They also advised that ephedrine-containing products not be used for more than 7 consecutive days (1).

Scientific Evidence

Herbal weight loss products have often contained ephedra alkaloids as the main effective ingredient. Research into the efficacy of ephedra, or ephedrine, and other compounds used for weight loss has produced 44 controlled trials to assess their effectiveness (2,3). When ephedrine was compared to placebo, only high doses of ephedrine produced a weight loss that was statistically significantly greater than zero. Ephedrine and caffeine versus a placebo did not produce a weight loss that was statistically significantly different between the groups after an average trial of 4 months. Ephedrine and caffeine vs. ephedrine had only 3 trials and showed that the ephedrine plus caffeine groups lost an average of 0.4 kg per month above weight lost with ephedrine alone. And lastly, ephedrine versus another weight loss formula demonstrated that at 15 weeks there were no statistically significant differences in weight lost between the groups. No long-term studies (one year or greater) using ephedrine have been conducted to determine its efficacy over time.

Studies that have evaluated ephedra alkaloids to determine their ability to enhance athletic performance have produced little data to support the claim (3,4,5,6). More studies have used a combination of ephedrine and caffeine or other stimulants and have demonstrated a modest improvement in aerobic and anaerobic performance (7-10). In a study designed to investigate the effects of caffeine, ephedrine, or their combination on muscular endurance during weight lifting found that subjects receiving the caffeine/ephedrine combination or the ephedrine alone had a significant increase in the mean number of repetitions completed (10). When time to exhaustion was considered, most studies found that the combination of ephedrine and caffeine improved time to exhaustion significantly over placebo or either stimulant alone (7-9). A randomized controlled trial evaluating performance on a cycle ergometer test showed that supplementation with caffeine (5 mg/kg) or ephedrine (1 mg/kg) extended time to exhaustion by approximately 1.5 minutes compared with placebo (8). A combination of caffeine and ephedrine, however, extended time to exhaustion by 5 minutes.

There has been concern over the potential for ephedrine and caffeine to increase metabolic heat production in exercising persons. To explore the possibility, 10 subjects exercised at 40 C and 30% RH for 3 h or until rectal temperature reached 39.3 C or heart rate was 95% of maximal for 3 minutes (11). Subjects were given 5 mg/kg caffeine and 1 mg/kg ephedrine or placebo. Rectal temperature and tolerance time were not affected. Mean skin temperature was

lower with supplementation. It was concluded that subjects evaporated more sweat to balance the added heat production. The results suggest that an individual exercising in an environment that does not allow for appropriate heat dissipation may predispose themselves to heat-related injury.

As the popularity of ephedra products rose, so did the adverse events reported to the FDA. Serious side effects reported in ephedra users include palpitations, high blood pressure, heart attack, seizures, stroke, psychiatric disturbances and even death. These reports prompted the National Institutes of Health to conduct a systematic review of the scientific literature on ephedra efficacy and safety in weight loss and athletic performance enhancement (12). The report, called the RAND report, reviewed 16,000 adverse events and categorized each event into cases that were definitely related, probably related, possibly related, or not related to ephedra. One group of researchers reviewed 140 adverse events associated with ephedra alkaloids that were submitted between June 1997 and March 1999 (13). Thirty-one percent of the cases were considered to be definitely or probably related to the use of supplements containing ephedra, and 31 percent were deemed to be possibly related. Of the events considered definitely, probably, or possible related to ephedra, 47 percent involved cardiovascular symptoms, 18 percent involved the central nervous system. The most frequent adverse effect was hypertension and ten events resulted in death. Most of the researchers reviewing the severity of adverse events associated with ephedra alkaloids have concluded that they pose a serious health risk to some users (13,14,15). Based on the many adverse events, the FDA has banned ephedra.

Adverse Reactions

CNS: Confusion, dizziness, headache, nervousness, psychosis, seizure, CVA.

CV: Arrhythmias, cardiac arrest, myocardial infarction.

GI: Constipation

GU: Urine retention, uterine contractions

Skin: Exfoliative dermatitis.

The FDA warns that more than 800 adverse events and over 80 deaths have been reported from the use of ephedrine products. Recently the FDA banned all ephedrine products because of the dangers associated with its use. Before its ban, ephedrine-containing products had been removed from all military commissaries and exchanges, and placed on a list of banned substances of several athletic organizations.

Drug Interactions:

Ephedrine products interact with the following medications:

- Beta blockers: Increased risk of hypertension and enhanced sympathomimetic effect on the vasculature.
- MAO inhibitors: Combination may increase risk of hypertensive crisis.
- Phenothiazines: May cause hypotension and tachycardia.
- Theophylline: May increase risk of GI and CNS adverse effects.

Contraindications

Pregnant patients should avoid ephedra because of the risk of uterine stimulation. Diabetic patients should not consume ephedra due to its hyperglycemic effect. Patients with a history of cardiac disorders, hypertension, cerebrovascular disease, glaucoma, and prostatic enlargement should not use this product.

Comments

Federal officials on 30 December 2003 announced plans to ban dietary supplements containing ephedra because of continued health concerns about the product, and

warned consumers not to take products containing the stimulant. This is the government's first ban on a dietary supplement, and it came eight years after the FDA began receiving reports that ephedra could be dangerous.

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2. Chromium (Picolinate, Tripicolinate)

Sources

Glucose Tolerance Factor (GTF Chromium), GTF Chromium Picolinate, Chroma Ultra Chromium Picolinate, Chromax, and Protecol. Metabotrim, OverDrive, GlycoBar, Appeal Lite, and Breakbar, Cheat & Lean Fat Blocker, Chromic Fuel, GTF Chromium Polynicotinate.

Manufacturers often add chromium to vitamin and mineral preparations in various dosages. Chromium is found naturally in beer, brewer's yeast, mushrooms, oysters, and some organ meats.

Chemical Composition

Chromium is an essential trace mineral that exists in multiple forms. Chromium, in the trivalent form (Cr(III)), is an important component of a balanced human and animal diet: a deficiency of chromium causes disturbance to the glucose and lipids metabolism in humans and

animals. In contrast, hexavalent Cr (Cr(VI)) is highly toxic carcinogen and may cause death to animals and humans if ingested in large doses. Recently, concern about Cr as an environmental pollutant has been escalating due to its build up to toxic levels in the environment.

Mechanisms of Action

Chromium participates in glucose, amino acid, and free fatty acid uptake by cells by enhancing the action of insulin. In animals and humans chromium has been shown to be an active component of glucose tolerance factor (GTF), which forms a complex with insulin to enhance the activity of insulin. The GTF is synthesized endogenously by a pyridine-2-carboxylic acid metabolite of tryptophan.

Theoretically, adequate chromium levels, in combination with insulin, can delay the onset of fatigue during endurance exercise due to a sparing of glycogen and increased use of free fatty acids as an energy source. In addition, amino acids can be transported into muscle cells for protein synthesis, especially during bouts of resistance training. This should decrease muscle catabolism and allow for a more anabolic state, with an accompanying increase in lean body mass. Chromium picolinate has been shown to have phenformin-like activity, but only in individuals with insulin resistance; no improvements are seen with glucose uptake in non-insulin resistant persons. It is believed that chromium increases the rate of internalization of insulin within cells by improving cell membrane fluidity.

Reported Uses

Chromium is marketed as having the ability to increase muscle mass and fat-free mass and decrease body fat and to stabilize blood glucose levels while enhancing the body's reliance on fat for fuel. In particular chromium is promoted as an essential supplement for persons with diabetes. Chromium picolinate is also marketed for suppressing appetite and cravings. Advertisements suggest that if chromium is taken with exercise and as part of an energy-controlled diet, the results can be outstanding.

Dosage

Chromium is an essential nutrient with an estimated requirement of about 1 µg/day. Because only 1 to 3% of trivalent chromium is absorbed, the Food and Nutrition Board of the NAS/NRC has stated that a safe, adequate intake of chromium for an adult is 50-200 µg/day.

When taken as a supplement, amounts up to 1 mg/day have been used. However, dosages should not exceed 800 µg/day, because such doses for an extended period can cause liver, kidney, and possibly muscle damage.

Scientific Evidence

Chromium has been studied for over 50 years and yet no well-defined methods for assessing chromium needs has been ascertained. Many studies have evaluated the effects of chromium on body composition and performance (1-12) and insulin sensitivity (13-16). Studies conducted to determine the efficacy of chromium for manipulation of body composition, improvements in strength, and cholesterol reduction have produced conflicting results. One study found that supplementation with chromium picolinate (200-400 µg/day) for two to three months resulted in significant losses in body fat and lowering of the insulin response to an oral glucose load (5). In one such study, 36 obese subjects were given either chromium yeast or chromium picolinate during and after weight reduction with a very low calorie diet (2). The treatment period lasted 26 weeks (8 wks of diet and 18 wks of maintenance), and the results showed that the chromium picolinate supplemented group increased lean body mass, whereas the other groups had a reduction in lean body mass.

Studies combining chromium with exercise found a significant loss of body weight for both the chromium group and placebo group but the chromium group had a significantly greater fat loss, in combination with a preservation of lean body tissue (1,5,7,8). Some controlled, double blind trial evidence is in conflict with these findings (3,5,10). Even a recent controlled trial evaluating the effect of chromium supplementation on resistance training in 18 men, failed to find a benefit of chromium on muscle size, power, strength, or lean mass (8). Another study investigated the efficacy of chromium, caffeine, dietary fiber, and CHO supplementation for maintenance of weight loss in the long-term(9). After the 16 month trial, the amount and course of body weight gain was equal for the supplement and placebo groups. Also no difference in body composition was found at the end of 16 months.

Several studies have pursued a role for chromium in the management of diabetes (14-16). It is theorized that chromium increases the rate of absorption of insulin within the cells by improving cell membrane fluidity. The majority of evidence does suggest that chromium can lower fasting blood glucose levels (14,15,16). In a study where subjects were given 1,000 µg of chromium per day, symptoms of type 2 diabetes were alleviated, and HbA1C levels returned to normal range.

Some trials have reported favorable changes in lipid profiles with the use of chromium. Doses in the range of 600 mg/day appear to produce the most beneficial results. Persons who are chromium deficient may be the best candidates for chromium supplementation to improve lipid profiles. Although conflicting data exist, a trial of 19 non-obese subjects receiving 1,000 µg/day of chromium or placebo for 8 wks failed to identify any significant difference between chromium and placebo groups with regard to measurements of lipid levels, body composition, and insulin sensitivity (16).

Overall, chromium appears to result in small, but non-significant, gains in lean body mass and muscle strength when taken in doses between 200 and 1,000 µg/day for 6 to 12 weeks (1). However, there does not appear to be an effect in older men and women (7,8). With respect to performance, no positive results of chromium supplementation on muscle strength with resistance training have been demonstrated as compared to placebo (7,8).

Whereas some clinical studies suggest that daily chromium supplementation (400 -1000 µg/day) may favorably affect insulin and glucose levels (14,15), not only in diabetics, but also in obese, insulin-resistant subjects (16), not all studies are positive. In 1999 the NIH convened a panel, which concluded that, at least for the general public, current data do not warrant routine use of chromium supplements, until the risk-benefit ratio has been adequately characterized.

Adverse Reactions

Although these reactions have been reported in association with chromium, a causative role cannot be assumed.

CNS: Cognitive impairment, headaches, insomnia, mood changes

GI: Diarrhea, epigastric discomfort, flatulence, nausea

GU: Renal failure

Hematologic: Anemia

Hepatic: Hepatic dysfunction/failure

Musculoskeletal: Motor dysfunction, rhabdomyolysis (18)

Drug Interactions

- Antacids: May bind dietary chromium, impairing absorption of chromium. Stagger doses.
- Antibiotics: May bind chromium and decrease absorption of the antibiotic. Recommend discontinuing chromium during antibiotic therapy.
- Vitamin C: May enhance chromium absorption. Consider lower dose of chromium
- NSAIDs: Use of NSAIDs may increase absorption of chromium.
- Corticosteroids: May increase urinary excretion of chromium;
- H₂ Blockers and Proton Pump Inhibitors: May decrease absorption of chromium.
- Insulin: When used together may increase risk of hypoglycemia

Contraindications:

Do not give to patients who are hypersensitive to chromium or the picolinate salt. Ingestion of chromium in excess of the RDA during pregnancy should be avoided. Do not take when renal or psychiatric conditions are present.

Comments

Studies conducted to determine the efficacy of chromium for diabetes, manipulation of body composition, improvements in strength, and cholesterol reduction have produced conflicting data. Most of these studies utilized small numbers of subjects, were not well-controlled, randomized trials, and used subjective measuring techniques. More recent clinical trials that used a more rigorous design and with adequate controls, failed to find significant improvements in any of the marketed uses with chromium supplementation.

The Federal Trade Commission charged Nu Skin International, Inc of unfair marketing practices for their making unsubstantiated statements about fat-loss, muscle-maintenance and other claims for supplements containing chromium picolinate. Nu Skin International, Inc., agreed to pay a \$1.5 million civil penalty to settle the charge.

Chromium can be toxic (17). A 24-year-old body builder developed rhabdomyolysis after ingesting 1.2 mg of chromium picolinate (6-24 times the daily recommended allowance of 50-200 µg) over 48 hours. This may be the first reported case of chromium-induced rhabdomyolysis (18).

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3. Chitosan

Sources

Chitosan, a nondigestible fiber, is found in the shells of crabs, lobsters, and other crustaceans. It is extracted and prepared in supplement form for products such as: Chitosan-C, Chitorich, Fat Breaker, and Fatsorb. Chitosan is also found in the fungal kingdom, invertebrate animals, brown algae, and in some higher plants.

Chemical Composition

Chitin is an aminopolysaccharide that is structurally similar to cellulose. The chitin, primarily derived from shells of shellfish, is deacetylated to form Chitosan, a dietary fiber.

Mechanisms of Action

Chitosan is a positively charged compound that attracts and binds negatively charged fatty acids, bile acids and phospholipids, which prevents their digestion and storage. The chitosan must be in the digestive system at the same time as the fat to block absorption.

Reported Uses

Chitosan is recommended for reducing fat absorption, lowering cholesterol levels, promoting weight loss, improving anemia, and for enhancing physical strength, appetite, and sleep. Chitosan is also used topically for treating periodontitis and promoting donor site tissue regeneration in plastic surgery.

Dosage

Typical recommendations range from 2-6 grams per day. Most clinical trials have utilized 2-3 g/day.

Scientific Evidence

When chitosan is consumed in the absence of a low calorie diet there does not seem to be an effect on weight loss (1-5). One study was designed to investigate chitosan as a possible adjunct therapy in the complex management of obesity (3). Fifty obese women were placed on a low calorie diet (1,000 kcal/day), given a supplement of chitosan (750 mg) and were followed for six months. Significantly greater amounts of body weight loss were reported in the chitosan group (15.9 kg) as compared to the placebo group (10.9 kg). Other studies report a plausible theoretical basis for chitosan as an effective weight loss supplement, however, there have been no human studies to prove effectiveness in the absence of diet control (4).

Research conducted in animals has shown promise for chitosan as an effective fat binder. In one study, rats were fed a very high fat diet in combination with high doses of chitosan. The results showed that fat absorption was reduced by almost 50% (6). In humans, the fat binding effect of chitosan has not shown the same results. In two separate studies, chitosan was given to subjects to measure the change in fat absorption (6,7). In both studies chitosan did not increase fecal fat content and therefore did not block fat absorption.

Animal and human studies examining the effectiveness of chitosan for hypercholesterolemia are mixed (1,2,3,9,10). Studies indicating positive effects of chitosan on cholesterol report as much as a 42% reduction in total cholesterol and a 35% reduction in LDL cholesterol (9). However, the majority of the studies report no effect on total cholesterol or LDL cholesterol (1,2,3,10).

Adverse Reactions

GI: Constipation, gas, bloating.

Other: Persons with allergies to shell fish should use cautiously.

Drug Interactions

No specific drug interactions have been documented, but carnitine may inhibit the absorption of some drugs and fat-soluble vitamins.

Contraindications

Pregnant and breast-feeding patients should avoid using chitosan because the effects are unknown. Chitosan should be used with caution by patients who have shellfish allergies.

Comments

Most of the research on chitosan has been conducted with animals. There seems to be a consensus that chitosan does bind to fatty acids/lipids in the digestive tract to prevent or minimize their absorption. In research conducted on animals and humans, no significant weight loss benefit has been noted. Researchers suggested that even though chitosan blocked fat absorption in research participants, the participants consumed more calories throughout the day from other sources to make up for any energy reduction. Although not all data are consistent, several animal and human studies have shown significant decreases in serum levels of LDL cholesterol with the use of chitosan.

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4. L-Carnitine

Sources

Carnitine is naturally occurring in meat and dairy products, and can be found in most amino acid and weight loss supplements.

Chemical Composition

An amino acid that is synthesized in the liver and kidneys from lysine and methionine. The “L” isomer of carnitine is the active form.

Mechanism of Action

Carnitine facilitates free fatty acid transport into the mitochondria of skeletal and cardiac muscle cells for use as fuel. Carnitine also serves a role in beta oxidation of fatty acids, and in maintaining the requisite ratio of fatty acetyl-CoA to free CoA for the Krebs Cycle. In addition, carnitine helps regulate the activity of pyruvate dehydrogenase, a key enzyme in glucose metabolism. Theoretically, increasing levels of carnitine could spare muscle glycogen and extend endurance performance. Carnitine could also reduce lactic acid accumulation in muscles by buffering pyruvate, which should extend time to fatigue.

Reported Uses

Carnitine is used for the enhancement of lean body mass, increasing reliance on free fatty acids as fuels (“fat burning”), improving aerobic performance, and lowering cholesterol and triglyceride levels.

Dosage

Studies have used doses of 2-6 g/day for 6 months with no adverse side effects. Most manufacturers suggest 2-6 g/day for enhanced athletic performance and weight loss. The recommended dosage for cardiovascular protection is 2 g/day. Must be certain it is L-carnitine, because either D, or D,L carnitine could lead to symptoms of L-carnitine deficiency.

Scientific Evidence

Studies exploring the effectiveness of L-carnitine on physical performance have widely differed on their outcome. One study considering L-carnitine supplementation on physical performance and energy metabolism gave seven endurance-trained athletes 2 g of carnitine 2 hours before the start of a marathon and at the 20 km mark (1). The researchers reported no significant change in marathon running time, R-values, plasma concentrations of glucose, lactate, and pyruvate, and fat metabolites. Also, there was no difference in a submaximal run test

conducted the following morning. Another study looked at carnitine and physical exercise to determine if carnitine supplementation would result in improved physical performance (2). The results indicated that carnitine supplementation did not enhance free fatty acid oxidation or spare glycogen, improve physical performance, decrease body fat or total body weight, nor increase $\text{VO}_{2\text{max}}$. The author concluded that athletes are not typically carnitine deficient and do not have an increased need for carnitine; thus supplementation would not improve exercise performance. A paper finding a beneficial effect to carnitine supplementation studied ten trained young men consuming either 2 g of carnitine or a placebo, one hour before a cycle ergometer test (3). The subjects taking carnitine had a significant increase in $\text{VO}_{2\text{max}}$ and power output, but carbon dioxide production, pulmonary ventilation, and plasma lactate were reduced. Under the conditions of this experiment, supplementation with L-carnitine showed an improvement in aerobic processes that resulted in a more efficient performance.

For weight loss, animal studies using L-carnitine have shown a positive effect (4,5). When obese cats were fed carnitine and consumed a restricted diet, weight loss was significantly more rapid than in cats given the placebo (4). Another study considered the effect of caffeine, carnitine, and choline, with and without exercise, on changes in rat body weight, fat pad mass, and leptin concentration (5). This study found that regardless of exercise, triglyceride level was decreased, whereas, serum leptin and body weight was lowered with supplementation and exercise. Studies involving human subjects did not show the same efficacy for carnitine as animal studies (6,7). Thirty-six overweight women received either 2g carnitine twice daily or a placebo for 8 weeks (6). All subjects participated in a 30 min walking program, 4 days/week. No significant changes in mean total body mass, fat mass, and lipid utilization occurred over time. Another paper comparing the effectiveness of several weight loss supplements found that no scientific evidence exists supporting the value of carnitine for weight loss (7).

Studies using L-carnitine in patients with cardiovascular disease have shown it to have a therapeutic effect (6,7,10,11). One study included two hundred patients with exercise-induced stable angina; they were each given 2 g carnitine daily for six months (8). The patients in the treatment group showed a significant reduction in number of PVCs, increased exercise tolerance, improved cardiac function and decreased plasma lipid levels. Carnitine has also been shown to be efficacious in increasing exercise tolerance in post-infarction, and reducing ECG indices of ischemia in stable effort-induced angina (9). Moreover, L-carnitine administration significantly improved the three-year survival rate of patients with heart failure and myocardial infarction (10,11). These studies concluded that L-carnitine represents an effective treatment for cardiac patients with post-infarction ischemia, cardiomyopathy, heart failure, and exercise-induced angina.

Adverse Reactions

GI: Nausea, vomiting, and stomach cramps.

Drug Interaction

- None known.
- If a patient ingests too much of the “D” isomer, carnitine could be displaced from the tissues and lead to muscle weakness.

Contraindications

No contraindications noted.

Comments

Most studies found no changes in fatty acid utilization or endurance performance with increased intake of L-Carnitine. Athletes observing a vegetarian diet may not consume adequate levels of carnitine and could benefit from supplementation. For patients needing cardioprotective benefits, supplementation may assist in maintaining the blood lipid profile and promote fatty acid utilization in the heart muscle.

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5. Hydroxy-Methyl-Butyrate (HMB)

Sources

HMB is found in small amounts in certain foods, including catfish, alfalfa, milk and grapefruit. It is also produced naturally in small amounts by the body, depending on dietary intake of protein and leucine: approximately 5% of the leucine in the body each day is converted to HMB to yield between 0.2 to 0.4 g a day in a 70-kg individual (1). Many products containing HMB are marketed, including Betagen, HMB Complex and capsules, Mass Action - Met-Rx, Amino Fuel Stack, Growth Fuel, Juven, CELL-MAX and others.

Chemical Composition

Beta-hydroxy-beta-methylbutyrate (HMB) is a metabolite of the branched chain amino acid, leucine. The HMB derivative of leucine is believed to be the active form of leucine.

Mechanism of Action

Leucine is recognized as serving a major role in regulating protein metabolism in skeletal muscle (1-10). It has been postulated that HMB may be the active compound associated with the anti-catabolic effects of leucine and its metabolites. Thus, increasing HMB in the diet

should promote muscle growth. with the end result being a reduction in the catabolism of muscle protein and preservation of fat-free muscle mass during intense training. It has also been suggested that HMB supplementation may provide protection against the physiological effects of overtraining. Since HMB supplementation may preserve muscle protein, it may prevent decreases in muscle strength due to overtraining.

Reported Uses

HMB is marketed as increasing protein synthesis and lean body mass, decreasing body fat and blood cholesterol levels, and accelerating muscle repair. HMB is also claimed to influence strength and lean body mass by acting as an anti-catabolic agent to minimize protein breakdown and damage to myocytes that may occur with intense exercise.

Dosage

Varies according to training intensity, 1-3 grams daily in one to three doses. Doses greater than 3 g/day do not promote strength or fat-free mass gains.

Scientific Evidence

Several recent research studies using HMB in combination with resistive exercise regimens have shown a positive effect on strength and lean body mass (1-9). In one study the effects of HMB were examined in 39 men and 36 women between the ages of 20-40 who were randomized to placebo or supplement plus a resistance training protocol (5). Participants trained three times per week for 4 weeks. The HMB group had a greater increase in upper body strength, increased fat-free weight, and decreased percent fat as compared to placebo. Another study considering HMB supplementation combined with strength training randomized subjects to three levels of HMB (0, 1.5 or 3.0 g) per day and two protein levels (117g or 175 g) and weight lifted for 1.5 hr, 3 day/wk for 3 wks (1). HMB supplementation significantly decreased the exercise-induced rise in muscle proteolysis and plasma creatine phosphokinase, an indication of decreased muscle damage and proteolysis (1).

HMB has also been tested on an older adult population to determine efficacy in increasing strength and fat-free mass during resistive training (9). Thirty-one men and women were randomly assigned to placebo or HMB 3 g/day for 8 wks while participating in resistive exercises 5 d/wk. HMB supplementation increased fat-free mass and amount of body fat lost for the HMB group as compared with placebo.

It also appears that HMB may protect against muscle damage. In one study participants took 3 g of HMB each day for 6 weeks while undergoing intensive training. After 6 wks all participants completed an endurance run, and those in the HMB group had significantly attenuated rises in creatine kinase as compared to the placebo group (10). HMB has also been shown to lower levels of creatine phosphokinase (CK) and lactate dehydrogenase (LDH), and decrease the excretion of 3-methylhistidine (3-MH), all markers of muscle damage/protein breakdown. Thus, HMB might also prevent or decrease muscle membrane inflammation or injury, and prevent increased proteolysis often associated with intense exercise (1,5,10). In summary, the HMB-induced decrease in muscle damage appears to be a consistent finding.

Finally, several studies have been conducted to evaluate it's safety (11,12). In one study, data were collected from nine studies in which humans has been fed 3 g of HMB per day (11). The studies were from 3-8 week in duration, included males and females, young and old, and exercising or non-exercising. The results of blood chemistry and hematology showed that HMB did not adversely affect any marker of tissue health and function. Similar findings were reported in another study (7). Overall, HMB appears to be quite safe.

Although much of the literature indicates HMB supplementation has a positive effect on muscle growth and strength (1-9), some researchers claim the literature is preliminary and often does not appear in peer reviewed journals (2,4). Questions regarding methodology, subject selection, and duration of the studies have also been raised.

Adverse Reactions

No adverse reactions have been noted from animal or human studies with doses as high as 4 g/day.

Drug Interaction

None reported.

Contraindications

None reported.

Comments

Many products sold as HMB also contain creatine monohydrate, L-glutamine, and/or N-Acetyl-Cysteine.

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6. Pyruvate

Sources

Most dietary supplements combine pyruvic acid with a mineral such as calcium or magnesium to improve stability. Trade names for pyruvate include Pyruvate, Metabolic Booster, Pyruvate Fuel, ATP-Fuel, Calcium Pyruvate, BioSculpt, Diet -Pyruvate, Pinnacle Pyruvate, and many others.

Chemical Composition

Pyruvate, the salt form of pyruvic acid, a 3-carbon molecule, can also be called 2-oxypropanoic Acid, acetylformic acid, alpha-ketopropionic acid, calcium pyruvate, magnesium pyruvate, potassium pyruvate, proacemic acid, and sodium pyruvate.

Mechanisms of Action

Pyruvic acid, formed in the body by the breakdown of glucose into 2 pyruvic acid molecules in the end stages of cellular glycolysis, is used in many metabolic pathways. It can be converted to lactate under anaerobic conditions and/or mass action reactions, or broken down to water and carbon dioxide. The conversion of pyruvate generates large amounts of ATP. In the presence of sufficient oxygen, pyruvic acid can be converted to acetyl CoA in the mitochondrion of the cell to produce energy. It is theorized that supplementation with pyruvic acid will enhance the cell's ability to generate energy and decrease CHO oxidation.

Reported Uses

Advocates claim that pyruvate will enhance weight loss, decrease appetite and fatigue, as well as increase energy levels, exercise endurance, and muscle glycogen stores.

Dosage

Most manufacturers recommend 3-15 g/day. A majority of weight loss studies have used 22 to 44 g/day and in some cases, more. Commercial preparations typically contain 500 mg to 1 gram of pyruvate with a recommendation of 2-3 administrations per day.

Scientific Evidence

The scientific evidence supporting pyruvate as a weight loss aid or an energy booster is somewhat controversial. A review article which compared various weight loss supplements showed pyruvate to be effective at high doses but little mechanistic information to explain its purported effect or data to indicate effectiveness at lower dosages (1). When pyruvate and dihydroxyacetone (DHA) were chronically fed to rats, the amount of weight gain and body fat content was significantly reduced during growth (2). The change in growth pattern was presumed to be caused by an increased energy loss as heat at the expense of fat storage. The rats showed a reduction in cholesterol levels, blood pressure and heart rate and increased time to fatigue on treadmill running. The researchers suggested the increase in performance following pyruvate supplementation was a result of increased reliance on blood glucose, thus sparing muscle glycogen.

Several human studies have shown that using pyruvate and dihydroxyacetone over various lengths of time can help improve endurance performance and aid weight loss (1-7). The effects of pyruvate on cholesterol levels and body composition were evaluated in hyperlipidemic patients consuming a low-cholesterol, low-fat diet (6). Thirty-four subjects were randomly assigned to receive 22-44 g pyruvate or placebo for 6 wks. Despite greater weight and fat losses with pyruvate, total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were not different between the two groups. In another study, 13 obese women consumed a low-calorie diet for 3 weeks while supplementing with pyruvate and DHA. The supplement group showed a greater loss of weight and fat as compared to placebo (7). The effects of pyruvate on the prevention of weight regain instead of weight loss has also been evaluated (8). Seventeen obese women were fed pyruvate and DHA or a placebo after completing a weight loss program consisting of a low-calorie diet. The subjects were given a diet providing 50% more energy than their calculated requirements. Results indicated that weight and fat gain were significantly less in

subjects receiving the supplements compared with the placebo group. They concluded that with the addition of 3-carbon compounds to a diet, weight regain could be minimized.

Finally, although there is evidence that persons who consume pyruvate tend to lose more fat and weight as compared to controls, the results have been exaggerated by enthusiastic marketers at several supplement companies (8).

Adverse Events

GI: Minor gastrointestinal disturbances, such as diarrhea and flatulence, with relatively high doses.

Drug Interactions

None reported.

Contraindications

Persons with known GI problems should limit the dosage.

Comments

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7. Synephrine

Sources

Synephrine is the active compound found in the fruit of a plant called *Citrus aurantium*, an orange tree native to China. The fruit is also called zhi shi or Chih-shih in China, and as green orange, sour orange and bitter orange in other parts of the world. The bitter orange fruit, peel, and juice contain the stimulant synephrine. Synephrine can be found in over-the-counter cold remedies, and in weight loss and energy enhancement supplements. Some common product trade names containing synephrine are: Neosynephrine, Thermogenic Formula, Citrus Slender, Bitter Orange, Avantra Z, Herbal Phen Fuel, and X-treme FX.

Chemical Composition

Synephrine is an alkaloid similar in structure to ephedrine, with one of the ring carbons hydroxylated and a side chain methyl group replaced by hydrogen.

Mechanisms of Action

Synephrine interacts with the CNS to produce a stimulant effect. The major site of action is the alpha-adrenergic receptor, with much less affect on the beta-adrenergic receptors.

The action on adrenergic receptors for synephrine appears to be more selective (alpha-1 and 2, and beta-3 only) than for ephedrine and thus may not produce the same cardiovascular side effects (1). Because of the stimulate effect similar to ephedrine and caffeine, synephrine is thought to boost energy, suppress appetite, and increase metabolic rate and caloric expenditure.

Reported Uses

Synephrine has been purported to increase metabolic rate and caloric expenditure, promote fat burning, weight loss, and increase energy levels. Bitter orange peel and fruit are used for nasal congestion, the flower and its oil are used for gastrointestinal problems, regulating blood lipids, lowering blood sugar, and stimulation of circulation.

Dosage

Citrus aurantium is made of several compounds and thus a standardized extract of synephrine is recommended. A typical standardized dose is 4-20 mg/day of synephrine which is contained in products espousing 200-600 mg of standardized citrus aurantium extract. The typical dose of bitter orange peel is 4-6 g/day of the dry peel.

Scientific Evidence

Very few scientific studies have examined the efficacy of synephrine with regard to weight loss. One animal study using rats considered the hemodynamic effects of synephrine treatment in portal hypertensive rats (2). In this study, synephrine significantly ameliorated the hyperkinetic state in both portal vein ligation and bile duct ligation rats. The mean arterial pressure in both groups was significantly reduced, as well as, systemic and portal vascular resistance. The study concluded that an eight-day administration of synephrine had a beneficial hemodynamic effect in both groups of rats. A human study was conducted to determine the cardiovascular effects of synephrine on normotensive adults (3). Subjects consumed 8 ounces of Seville orange juice and water in a cross-over method followed by another ingestion 8 hours later. A significant increase in heart rate, systolic and diastolic blood pressures and mean arterial pressure was noted in response to ingestion of the Seville orange juice.

In a review by Preuss et al. (2), a double blind, placebo-controlled, randomized study using a combination of Citrus aurantium, caffeine and St. John's Wort, in combination with a restricted diet was described. Participants receiving the supplement combination had significantly greater fat losses, but not weight losses as compared with placebo and controls (2). The review also describes a study involving female participants who were given no supplement the first week of a weight loss regime and Citrus aurantium the second week. During the first week, the mean weight lost was 0.94 kg, whereas during the second week, mean weight loss was 2.40 kg (2). The researchers felt this was significant because typically more weight is lost in the first week of a diet protocol, even if only attributed to water loss. In sum, although, Citrus aurantium may be a reasonable thermogenic agent, more studies are needed to establish this definitively, and determine the risks used under various physiologic stressors.

Adverse Events

No adverse events have been reported. Synephrine has been shown to increase blood pressure in animal studies.

Drug Interactions

- Beta blockers: Increased risk of hypertension and enhanced sympathomimetic effect on the vasculature. Avoid Synephrine products
- MAO inhibitors: Combination may increase risk of hypertensive crisis. Avoid Synephrine products.

- Phenothiazines: May cause hypotension and tachycardia. Avoid Synephrine products.
- Theophylline: May increase risk of GI and CNS adverse effects. Avoid Synephrine products.

Contraindications

Not recommended for persons with cardiovascular disease, especially hypertension, tachyarrhythmias, and narrow-angle glaucoma and monoamine oxidase inhibitor recipients should avoid consumption. Persons taking decongestant-containing cold preparations should also avoid. It is not recommended for children or for women who are pregnant or lactating.

Comments

This particular product shows promise, but well-designed studies need to be conducted under various conditions and in diverse populations.

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8. Hydroxycitric Acid (HCA)

Sources

Rind of the fruit *Garcinia cambogia* native to India and Southeast Asia. A number of dietary supplements contain *Garcinia* extracts under the names of Citrin, Citrimax, and Regulator HCA.

Chemical Composition

The rinds of the *Garcinia cambogia* fruit are dried and cured in preparation for extraction. When the rind is dried to a brown color, about 10-30% of the weight of the dried rind is HCA. Synthetically produced HCA is also available and is claimed by manufacturers to contain the exact chemical structure as naturally occurring HCA.

Mechanisms of Action

HCA can block the enzyme in cells that converts CHOs to fat. If HCA blocks the conversion of citrate into acetyl-CoA, then in theory it would suppress fat synthesis. If conversion of CHO to fat is blocked then the excess CHO must go somewhere. It is theorized that the body must dispose of excess CHO by metabolizing or storing them. If stored as glycogen, the fully loaded stores may suppress appetite and thereby reduce food intake and promote weight loss.

Reported Uses

Claims for HCA include weight loss, fat burning, and increased energy levels.

Dosage

For loss of body weight and appetite suppression the typical dose is 750-1500 mg of *Garcinia cambogia* (at least 50% HCA) taken in 2-3 divided doses before meals.

Scientific Evidence

Animal studies have shown that HCA has a suppressive effect on appetite, energy intake, and weight regain (1,2). In one study rats, after 10 days of restrictive feeding, were fed

either a diet of 1% fat or 12% fat, both supplemented with 3% HCA (1). Only rats fed the 12% fat diet plus HCA had long-term suppression of food intake. However, the suppressive effect of HCA on body weight regain, which was maintained for more than 3 wks, was independent of dietary fat content. Another animal study considered the acute and chronic effects of HCA on energy metabolism in mice administered 10 mg HCA or placebo twice daily for 25 days (2). The mice were run for 1 hour on day 26 and respiratory gases were measured. The respiratory exchange ratio was significantly lower in the HCA group during both resting and exercising conditions. The results suggested that HCA may promote lipid oxidation and spare CHO utilization in mice.

Studies in humans have had mixed results. In an 8-wk double blind placebo-controlled trial of 60 overweight individuals, use of HCA at a dose of 440 mg, 3 times/day produced significant weight loss as compared to placebo (3). A 6 wk randomized placebo-controlled trial with 24 subjects gave a placebo for 2 wks and then administered 300 mg HCA for 2 wks (4). HCA administration resulted in a decrease in energy intake by 15-30% without changes in appetite and mood, while body weight tended to decrease. Similarly, a 12 week double blind trial reported that HCA (2.4 g *Garcinia cambogia* per day) also had no effect on appetite (5). In contrast, a 12-week double blind placebo-controlled trial of 135 overweight individuals, who were given either placebo or 500 mg of HCA 3 times/day, found no effect on body weight or fat mass (6). However, this study was criticized for using a high-fiber diet, which is thought to impair HCA absorption (7,8).

With respect to performance, the acute effects of HCA supplementation on substrate utilization were investigated in endurance-trained athletes. Trained cyclists ingested 3.1 mL/kg body wt of HCA solution or placebo and exercised for 1 hour (9). The HCA, even when administered in large quantities, did not increase total fat oxidation in endurance-trained athletes. Overall, the data do indicate that HCA may offer a low-risk approach for weight loss, but not performance enhancement.

Adverse Events

GI High doses can cause GI distress.
No other adverse events reported.

Drug Interactions

None noted.

Contraindications

Not recommended for children or for women who are pregnant or lactating.

Comments

Should be looked into further. May have great promise for weight loss.

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9. Conjugated Linoleic Acid (CLA)

Sources

Conjugated linoleic acid (CLA) is a naturally occurring fatty acid found in milk fat, beef, and meat of other ruminant animals. It is marketed as Tonalin CLA, CLA fuel and in many supplements under the label of CLA.

Chemical Composition

CLA is a mixture of positional and geometric isomers of linoleic acid, which is one of the omega 6 essential fatty acids, the other being linolenic acid. They are unsaturated fatty acids with double bonds occurring at carbons 10 and 12 or 9 and 11. The scientific names for CLA are cis-9,trans-11 conjugated linoleic acid; trans-10,cis-12 conjugated linoleic acid: these different isomers may have different physiologic effects.

Mechanisms of Action

CLA is an antioxidant, and as such, it protects cell membranes from oxidation by trapping free radicals. CLA may also act as an antimutagen and anticarcinogen by modulating the activity of cytochromes P450 and suppressing the activity of ornithine decarboxylase and protein kinase C, enzymes involved in carcinogenesis. Some researchers have theorized that it may also suppress protein and nucleic acid synthesis in cancer cells. It has been suggested that CLA might reduce body fat by promoting apoptosis in adipose tissue.

Reported Uses

CLA is purported to act as an antimutagen, antioxidant, cholesterol lowering agent, and many claim it the accretion of lean mass and loss of adipose tissue mass.

Dosage

A typical dose for weight loss ranges from 2 to 7 grams per day. Most research shows that doses greater than 3.4 grams per day do not confer any additional benefit.

Scientific Evidence:

Most of the studies using CLA have been conducted in animals. CLA has been shown to have positive effects on body fat, lean mass, and energy expenditure in the majority of these studies (1,2). In one study changes in feeding and induction of apoptosis in adipose tissue as a function of feeding mice a mixture of CLA isomers were investigated for 12 days (1). Dietary CLA reduced feed intake by 10-12% but did not increase energy expenditure or body weight. Apoptosis was increased in white adipose tissue by CLA consumption. In another animal study the influence of CLA on energy balance was examined in 48 mice assigned to one of two groups (energy restricted/non-restricted) and then half of each group was fed CLA or placebo for 39 days (2). The percent of energy intake expended as heat increased in the CLA group as compared to controls. The lower energy storage in the CLA group was a result of increased energy expenditure (74%) and an increase in the amount of energy lost in feces (26%). In yet another study, the effects of CLA on body composition, tissue lipids, and lipoproteins were examined in two groups

of rats fed 3g of CLA (or placebo)/100g feed for 3 weeks and then fed a weight-loss diet for 18 days (3). The rats fed the CLA diet gained 11% less weight, had less body fat and a higher deposition of lean body mass relative to controls. CLA fed rats also had 41% lower cholesterol concentration in liver, and significantly lower VLDL, with no change in LDL and HDL. Thus, at least in rats, CLA appears to alter body composition, independent of diet.

In contrast, the scientific evidence is almost evenly split between positive and no-effect studies in humans. In a double blind, randomized trial, 23 resistance-trained subjects were given a diet with 6 g CLA/day or placebo for 28 days to examine CLA's effect on body composition during resistance training (4). The results revealed that CLA supplementation did not significantly affect changes in body mass, fat-free mass, fat mass, percent body fat, strength, or general markers of catabolism during training. In another double blind placebo-controlled trial, 60 men with metabolic syndrome were randomized to a t10c12 CLA, a CLA mixture, or placebo for 12 wks (5). The t10c12 CLA supplementation increased oxidative stress and inflammatory biomarkers in obese men. The results indicated that the oxidative stress seems closely related to induced insulin resistance. Likewise in a trial using 17 women over a 64 d period, CLA had no significant effect on energy expenditure, fat oxidation, body composition, or RER at rest or during exercise (7). In contrast to these studies, a randomized, double blind placebo-controlled study in 20 healthy adults who participated in a standardized exercise routine for 90 min 3 times/wk consumed either placebo or 6 g CLA 3 times/day for 12 wks (6). Body fat was significantly reduced in the CLA group but there was no effect on body weight.

Adverse Events

GI: Gastrointestinal upset

Other: Fatigue.

Drug Interactions

None known. However, there has been some evidence that CLA might increase vitamin A storage in liver and breast.

Contraindications

Not recommended for children or for women who are pregnant or lactating.

Comments

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C. Testosterone Enhancers

1. Androstenedione

Sources

Also known as Andro, Androstene, and Norandrostenedione. Androstenedione is an intermediary in a chemical chain arising from cholesterol, and is produced by the adrenal glands and the gonads from either 17alpha-hydroxyprogesterone or dehydroepiandrosterone (DHEA). Endogenous production peaks in the 3rd decade of life and then declines steadily after age 30 (1). It also occurs naturally in animal foods and in the pollen of Scotch pine trees (10). Androstenedione supplements are sold in health food stores, and are classified as a dietary supplement. Of note the largest marketer of dietary supplements, General Nutrition Center, does not currently sell it due to controversy over its safety and a lack of long-term studies, however androstenedione is still widely available and relatively inexpensive.

Chemical Composition

4- or 5-androstene-3beta,17beta-dione. Analogs of androstenedione also available include 4- or 5-androstenediol and 4- or 5-norandrostene- dione or diol. It differs from testosterone by one hydrogen atom.

Mechanism of Action

Androstenedione, a relatively weak androgen with a very short half-life, is directly converted into either testosterone or estrone (an estrogen) in the blood. The conversion of androstenedione to testosterone is activated by luteinizing hormone and catalyzed by 17beta-hydroxysteroid dehydrogenase (1,2,3). The anabolic effects of testosterone are well documented. Gains in muscle size and strength occur and have been most consistent among subjects using anabolic steroids in conjunction with an adequate strength training program and a diet sufficient in nitrogen. These stated benefits appear to vary with the physical demands of the sport, with more benefit seen in strength-dependent sports such as weight lifting, shot put throwing, and football. The potential benefit is less for sports that require speed, flexibility, or endurance, but are still significant. A sense of euphoria or a decreased sense of fatigue during training is often reported by the athlete. These psychological effects may allow a higher intensity and longer duration of training.

Reported Uses

Supplementation is believed to elevate the endogenous production of testosterone in both males and females. This enhancement of anabolic steroids, when combined with a strength-training regimen leads to an improved gain in muscle size, strength, and reduction in body fat composition. The trainee is claimed to be able to endure greater and longer bouts of exercise, with shorter recovery time due to blunting of the catabolic effects of strenuous exercise. It has also been used to increase sexual arousal and libido.

Dosage

Androstenedione is recognized as a fast-acting, over-the-counter alternative to prescription-only steroids. It is sold in capsules or pills for oral use. The typical, suggested method of intake is to consume 50-200 mg of androstenedione once or twice per day. Sellers of androstenedione claim that when testosterone is produced through digestion the body can control

the amount produced. Thus the danger of getting too much testosterone and experiencing side effects is minimal; this is in contrast to the intravenous injection of anabolic steroids. Percutaneous gels, transdermal patches, and chewing gums are also available, and recently a liquid spray for sublingual use. The sublingual spray purportedly raises testosterone levels in less than 30 minutes. East German athletes snorted it as a nose spray an hour before competition in the 1988 Olympics (this was a team requirement). This apparently had no benefit on the athletes' performance, however, and many of them simply complained of sinus-headaches.

Many manufacturers of androstenedione suggest the supplement be consumed about an hour prior to exercise. Recommendations for longer term use include cycling the use of the supplement (e.g. four weeks on/one week off). Pyramiding, or increasing the dose throughout each cycle, may lead to doses that are 10 to 40 times greater than those used for medical indications. This agent may also be "stacked" i.e. taken along with a variety of other anabolic steroids and their precursors.

Scientific Evidence

Throughout its life span of over 60 years, no study has shown androstenedione to be of any significant benefit to athletic performance or to enhance anabolic activity. Studies have focused on 50-300 mg oral supplementations once or twice daily. Androstenedione plasma levels increase acutely, with a peak at 60-90 minutes, and decline after 270 minutes. Blood values remain above baseline with continued use. Interestingly, androstenedione does not seem to have any independent anabolic effects, and markers of muscle anabolism, physical strength, or lean body mass growth remain unchanged after supplementation. Furthermore, no studies have demonstrated changes perceived in mood, health, or libido (4,5,6,7,8).

Utilization of the supplement for periods of time less than one month can sometimes increase testosterone levels (1,6,9). However testosterone levels return to baseline (pre-supplementation) levels with continued use shortly, in conjunction with a decline in luteinizing hormone and an increase in DHEA concentrations. Available data suggest that androstenedione may therefore down-regulate testosterone synthesis (6,9).

In contrast to testosterone, androstenedione does appear to consistently increase estrogen levels (1,6,7,4,8,10), an event that may increase the risk of unwanted estrogenic side effects (see below) in both men and women. Of note, testosterone itself may be converted to the estrogen (Estradiol) by aromatase or dihydrotestosterone by 5alpha-reductase.

Some manufacturers include herbal aromatase and 5-alpha-reductase inhibitors in their products by claiming they temporarily inhibit the conversion of androstenedione and testosterone into estrogens. Such products, called "flavones" or "flavonoids" have a slightly higher affinity for aromatase *in vitro*, but no evidence exists that this process occurs in humans (10,11). Studies also confirm a consistent reduction in high-density lipoprotein (HDL) cholesterol when supplementing with androstenedione (6,10).

Adverse Reactions

CNS: Cognitive impairment, headaches, insomnia, mood changes

Endocrine: Excess estrogen, gynecomastia, hirsutism, virilization (12)

CV: Low HDL

GI: Diarrhea, epigastric discomfort, flatulence, nausea

GU: Decreased sperm production, testicular atrophy, prostate enlargement and cancer, breast cancer, menstrual abnormalities, unwanted masculinizing features

Hematologic: Lowering of HDL

Hepatic: Hepatic toxicity/dysfunction/failure

Musculoskeletal: Motor dysfunction, rhabdomyolysis, anabolic effects (18)

Skin: Acne

Drug Interactions

Taking androstenedione along with estrogen products may have a synergistic effect on increasing estrogen levels and estrogenic side effects.

Contraindications

Androstenedione should be avoided during pregnancy as it may induce labor, and not used during lactation given a lack of data.

Children should not use this drug given the potential of premature closure of bone growth plates.

Androstenedione may exacerbate testosterone and/or estrogen sensitive conditions. People with prostate cancer, breast, uterine, or ovarian cancers, BPH, endometriosis, or uterine fibroids should avoid its use (13).

Patients with liver disease should not take Androstenedione. Consider monitoring liver function tests (LFTs) in patients using this supplement.

Comments

The use of androstenedione supplements is banned by the International Olympic Committee, the National Football League, the National Collegiate Athletic Association, the National Basketball Association, and the World Natural Body Building Federation. It gained enormous popularity in 1998 after Mark McGuire acknowledged its use in his Major League Baseball home-run record setting year. MLB and the National Hockey League to date do not ban its use. An amendment to the Controlled Substances Act, known as The Anabolic Steroid Control Act of 2003, has been proposed by the Senate. The purpose of this Act is to clarify the definition of anabolic steroids and to provide for research and education activities relating to steroids and steroid precursors. The act has currently received Senate approval and is now in the assembly. The amendment, if passed, will limit the sale of Androstenedione and other anabolic steroid precursors to minors, with the noted exception of DHEA (14).

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2. Dehydroepiandrosterone (DHEA)

Sources

Dehydroepiandrosterone is also known as DHEA, GL701, and prasterone. It is available alone or in a number of combinations. Products with DHEA include Andro-6, ANDRO-Xtreme, Anotestin, Biogra, Gro Pro, Migrelief, Rejuvive, Ultimate Libido Formula for Women, and Viga.

**DO NOT CONFUSE with 7-keto-DHEA, or 7-oxo-DHEA, a metabolite of DHEA that increases metabolism and thermogenesis.
It cannot be converted to androgens or estrogens.**

DO NOT CONFUSE with Wild Yam extracts, which is touted as “Natural DHEA.” The hormone-like substance in the plant root, diosgenin, is a laboratory precursor for DHEA and other steroid compounds, but the transformation does not occur in the body.

Chemical Composition

DHEA is an androgenic hormone produced primarily in the adrenal glands. It functions as a precursor for the production of more than 50 other hormones in the body.

Mechanics of Action

ACTH triggers secretion of DHEA from the adrenal glands. DHEA levels are dependent upon both age and gender. Levels decline gradually starting in the 20's and sharply (up to 90%) at the adrenopause in the 40's or 50's. Female levels are consistently about 60% of those in males (1).

The conversion of DHEA to testosterone is a two-step process. The enzyme, 3 beta-hydroxysteroid dehydrogenase 5, 4-isomerase, irreversibly converts DHEA to androstenedione, and then 17beta-hydroxysteroid dehydrogenase converts this to testosterone. Although this is theoretically the route by which beneficial, ergogenic effects take place, DHEA supplementation appears to change the circulating androgen/estrogen ratio in a gender specific manner, so that in men, estrogen increases more than testosterone, and in women, vice versa. Other potential mechanisms include antagonization of gamma-aminobutyric acid (GABA) transmission, modulation of N-methyl-D-aspartate (NMDA) receptors, and NO release (1,2).

Reported Uses

DHEA is taken to slow or reverse aging, promote weight loss, boost immunity, improve mood, memory and sleep patterns, and increase strength, energy, muscle mass and sex drive. It is also taken to treat systemic lupus erythematosus (SLE), multiple sclerosis (MS), Addison's disease, depression, schizophrenia, chronic fatigue syndrome, erectile dysfunction, menopausal symptoms and atrichia pubis, and to prevent heart disease, breast or other cancers, and diabetes (1,3).

Dosages

Commercially available supplements range from 5-200 mg. Doses of 25-1600 mg/day have been used, but the typical dose is 25-100 mg/day (1-3).

Scientific Evidence

Men with erectile dysfunction (ED) may have improved sexual function on DHEA. One study demonstrated that oral DHEA (50 mg/day for six months) benefited men with ED who had hypertension and men with ED without an organic etiology (4). Those with adrenal insufficiency show some benefit in well-being, sexuality, and the quality of their skin and hair (1,5). Benefits have been seen in depression, diabetes and lupus (1,5). Whereas androstenedione concentrations are reported to be increased by DHEA, no changes in testosterone have been found (6). Older populations (>50 years old) have demonstrated some benefit from DHEA in terms of increased muscle mass, overall feelings of well-being, and immune system function (7,8,). No performance benefits have been reported. Although the data are limited, DHEA does not appear to be effective in individuals who are younger than forty (6-8).

Adverse Reactions

CNS: Irritability, aggressiveness, insomnia, headache, nervousness, mania, fatigue

CV: Hypertension, decreased HDL cholesterol

GI: Hepatic dysfunction, abdominal pain

Endocrine: Hirsutism, voice deepening, changes in menstrual pattern, insulin resistance, gynecomastia, prostatic hypertrophy, acne, hair loss

Drug Interactions

- Glucocorticoids: Glucocorticoids can suppress endogenous DHEA production. Conversely, DHEA may reduce the dose of glucocorticoids needed to treat SLE.
- Insulin: Insulin can decrease levels of endogenous DHEA-S.
- Antidepressants: DHEA may alter the effects of these medications and dose needed for treatment.
- Estrogen and estrogen-like medications: DHEA can be converted into the hormone estrogen, which may alter the effects of these medications and possibly the dose needed for treatment.
- Anticoagulant medications: DHEA affects the blood's clotting ability and may alter the effects of these medications or the dose needed for treatment.
- CNS: DHEA may act in the body like some of these medications, which may alter the effects of these medications and possibly the dose needed for treatment.
- Diabetic / Hypoglycemic medications: DHEA may alter the effects of these medications and possibly the dose needed for treatment.
- Drugs metabolized by cytochrome P450: DHEA may have a slight, probably subclinical, effect.

Contraindications

Because of the potential for conversion to testosterone or estrogen, DHEA could affect any hormone-sensitive cancer, including breast, uterine, ovarian, or prostate, or any hormone-related condition such as endometriosis, uterine fibroids, or prostatic hypertrophy.

DHEA may affect blood glucose levels in diabetes and exacerbate liver dysfunction. A number of exacerbations have occurred in psychiatric patients taking DHEA (1).

Comments

DHEA is a powerful steroid hormone and not a “natural medicine.” It can be classified as a dietary supplement only through a quirk of DSHEA, which allows any substance made in the body to be sold as a dietary supplement.

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3. Gamma Oryzanol

Sources

Gamma-Oryzanol, Gamma-OZ, Oryzanol, but found in many products, including Muscle Builder, Atkins Menopause, Chromium Picolinate Plus, Coreplex, GammaFrac, and Opti Fuel to name only a few.

Chemical Composition

Gamma oryzanol is a naturally occurring mixture of plant chemicals called sterols and ferulic acid esters. Specifically it is made up of cycloartenyl ferulate, 24-methylene cycloartanyl ferulate, and campesterol ferulate. Naturally it is derived from rice bran oil, but it is also found in corn and barley oils, wheat bran, oats, fruits and vegetables.

Mechanisms of Action

After ingestion, gamma oryzanol is taken up by the liver and broken into sterol and ferulic acid. The sterol is excreted, while the ferulic acid is thought to enhance secretion of growth hormone releasing hormone (GHRH) and thus human growth hormone (hGH), which would then enhance skeletal muscle accretion. Gamma oryzanol may also increase endorphin release which would help to minimize exercise induced fatigue.

Gamma oryzanol may lower cholesterol by decreasing cholesterol absorption (thereby increasing excretion) from the gut. Its effects on HDL levels are conflicting (1,2).

Reported Uses

The various uses of gamma oryzanol include muscle building, reducing muscle fatigue, increasing testosterone and GH levels, reducing total and LDL cholesterol levels,

increasing HDL level, mediating menopause and aging symptoms, relief of gastritis, and protecting against cancer.

Dosage

Dosages for gamma oryzanol range from 100-500 mg per day. It is often suggested that taking one to two tablespoons of rice bran or rice germ oil per day will provide the same amount of gamma oryzanol (One cup of white rice contains approximately 4 mg.).

Scientific Evidence:

Most of the studies with gamma oryzanol have come from Japan, given the vast production of rice bran oil in that country. Peer-reviewed studies on gamma oryzanol as an exercise performance enhancer are limited. In 1997, 22 college-aged males were recruited to ingest either 500mg of Gamma-oryzanol or placebo each day during a nine week periodized resistance exercise program (3). Body composition, muscle strength, power, heart rate, blood pressure, testosterone and lipid levels were compared, and although performance measures improved, no differences were noted for the gamma oryzanol and placebo groups, which indicated that ingesting gamma-oryzanol during a strength training regimen does not confer any benefit (4).

Some authors believe gamma oryzanol may actually have anti-anabolic (catabolic) effects because of evidence from rat studies that intravenous or subcutaneous injections of gamma-oryzanol suppress the release of luteinizing hormone, reduce growth hormone synthesis and release, and may increase release of the catecholamines, dopamine and norepinephrine, which could reduce testosterone production (1).

The antioxidant properties of gamma oryzanol and its derivative, ferulic acid, are promising in some areas. Although vitamin E (alpha-tocopherol, alpha-tocotrienol, gamma-tocopherol, and gamma-tocotrienol) is thought to be the major antioxidant in rice bran that reduces cholesterol oxidation, one study proposed that gamma oryzanol may actually be the major antioxidant factor, particularly given it is 10 times higher than vitamin E. Thus, gamma oryzanol may be the hypocholesterolemic property of rice bran (5). Other preliminary clinical evidence claims that gamma oryzanol can significantly decrease total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels (6). However, the effects of gamma oryzanol on high-density lipoprotein (HDL) cholesterol levels are conflicting: some show improvement (decreased HDL) in those with already elevated levels, and no improvement in patients with previously normal HDL levels (7,8).

Finally, some evidence indicates that gamma oryzanol can decrease serum TSH levels in patients with primary hypothyroidism (9), and other data support the use of gamma oryzanol in the relief of menopausal symptoms (10). However, more studies are needed for all of the reported uses (Refer to the section on Ferulic acids for more associated findings)

Adverse Reactions

If taken in doses up to 600 mg/day for several months it can cause dry mouth, sleepiness, hot flushes, irritability, and light headedness in some individuals.

Drug Interactions

None known

Contraindications

Insufficient evidence regarding its safety during pregnancy and when breast feeding are available.

Comments

Poorly absorbed (<10%) from the GI tract. Can reduce TSH concentrations in patients with hypothyroidism (1,2,9)

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4. Ferulic Acid

Sources

Ferulic acid is either found alone or as a component of multi-ingredient herbal supplements. Some of these include: Gamma FRAC, Trans-Ferulic Acid, Gamma Oryzanol, Powerhouse HGH Bodybuilding Formula, Ultra Vitality, NutraPack, IP6 Optimizer, FertilityBlend for Men, Amino Max, and Dong quai. It is also a natural component of Rice Bran Oil, raspberries, blueberries, blackberries, some citrus fruits, as well as being a component of plant cell walls.

Chemical Composition

Ferulic acid is a component of gamma-oryzanol. It is an ester-linked hydroxycinnamic acid (phenol based compound) with antioxidant properties, and it is found naturally in plant cell membranes, wheats, oats, rice, bran, and coffee.

Mechanisms of Action

Ferulic acid is believed to have antioxidant properties. As such, it may improve endurance and muscle building capacity by preventing the formation of free radicals in muscle tissue, which in theory could decrease muscle soreness and fatigue in response to anaerobic exercise. Ferulic acid may have direct anabolic effects, increase testosterone levels or act as a growth hormone stimulator. More recently it has been claimed that this free radical scavenging has antimutagenic actions.

Reported Uses

Ferulic acid is used for many reasons, to include anti-inflammatory activities, protecting against skin cancer, reducing muscle fatigue/pain, muscle building, fat burning, GI

cancer prevention, minimizing free radical damage, lowering cholesterol levels, improving sperm quality, enhancing fertility in women, having beneficial effects for the liver and lipid metabolism, minimizing effects of aging and common colds, and preventing nitrite formation.

Dosage

Ferulic acid supplements used in most research studies range from 30 - 50 mg per day. It is most often sold in 20 - 250 mg tablets, with recommendations for athletes to take one tablet 30 to 45 minutes before and after workouts. As a dietary enhancement, 1 to 2 tablets daily with meals is recommended.

Scientific Evidence

There is scant direct evidence to support the anabolic effects mentioned above (refer to the section on Gamma Oryzanol). Numerous studies cite ferulic acid either alone, as a component of Gamma-Oryzanol, or in combination with numerous other phorbol esters as having significant antioxidant properties (1). Some antioxidant actions specifically attributed to ferulic acid include: having an anti-atherosclerotic role by preventing the oxidation of LDL and its constituents (vitamin E, phosphatidylcholine) (2); inhibiting enzymes (alpha-amylase, trypsin, and lysozyme) (3); having a chemopreventive capacity possibly due to increasing the activity of the glutathione S-transferase detoxification enzymes (4); inhibiting iron-induced oxidative DNA damage (5); and inhibiting platelet aggregation induced by ADP and/or arachidonic acid (6).

Ferulic acid has also been shown to have lipid and triglyceride lowering capability, and it may slow the rate of weight gain in rats (7,8,9). It appears to exert a hypotensive effect via mediation of muscarinic acetylcholine receptors, and is associated with NO-mediated vasodilation(10). Ferulic acid also shows promise as an antimutagenic. One study found that topical application of a synthetically produced ferulic acid analog attenuated edema and papilloma formation (11). This analog (FA15) also suppressed lipopolysaccharide and interferon-gamma-induced protein expressions of NO synthase and cyclooxygenase-2, as well as inhibiting the release of tumor necrosis factor-alpha. These actions suggest an anti-inflammatory mediator role as well (11). Another study showed definitive photoprotective effects in human subjects (12). The antioxidant properties of grains are largely attributed to their phytochemical compounds, of which ferulic acid is the major phenolic compound. Interestingly, the benefit derived from including grains in one's diet is the prevention of colon, breast, prostate, and other GI cancers, as demonstrated in epidemiologic studies. Some animal research also support antioxidant actions (13,14).

Finally, ferulic acid even seems to hold promise in treating hot flashes in peri/post-menopausal women (15). Thus the roles of ferulic acid and other related antioxidants appear very exciting, but the research is incomplete. Future studies will likely differentiate the role of this particular and its mechanisms in the variety of uses proposed.

Adverse Reactions

None reported

Drug Interactions

None Known

Contraindications

Insufficient evidence for use during pregnancy, breast feeding

Comments

No side effects have been reported in animal studies utilizing doses up to 1500mg per day of ferulic acid (16). Little is known about the absorption of ferulic acids and similar polyphenols, with contradicting evidence as to whether free, bound, or both forms are best absorbed. It appears that the bioavailability of ferulic acid is determined primarily by its associated food matrix, its affinity for lipid substrates, and less so on its metabolism. Studies indicate a low bioavailability in cereals, but plasma concentrations of ferulic acid are increased between one and three hours after ingestion of cereal (1,14,17,19).

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5. Smilax: Sarsaparilla, Sapogenins, Smilagenin, and Sitosterol

Sources

Genus *Smilax* is commonly referred to as Sarsaparilla and includes the species *S. officinalis*, *S. japicanga*, and *S. febrifuga* from South America, *S. regelii*, *S. aristolochiaefolia*, and

S. ornata from Mexico and Latin America, and *S. glabra* from China. It is a perennial tropical American vine that grows up to 50 meters long, and is also known by the names Shot Bush, Small Spikenard, Wild Licorice, Black Creeper, and Rabbit Root. Jamaican Sarsaparilla is considered to be one of the finer varieties (1,2).

Chemical Composition

The root of sarsaparilla, the portion of the plant used for medicinal purposes, is 6 to 8ft long, tuberous, odorless and relatively tasteless. The majority of its pharmacological properties and actions are attributed to sterols and saponins. The root contains the plant sterols sarsapogenin, smilagenin, sitosterol, stigmasterol, and pollinastanol. About 2% of the root consists of the saponins, sarsapogenin and smilagenin. Other constituents include calcium, copper, iron, iodine, manganese, potassium, silicon, sodium, sulfur, vitamins A, C, and D, and B-complex (2,3).

Mechanisms of Action

The saponins in sarsaparilla may be responsible for its reputation as a cleansing agent, as they induce diuretic, expectorant, diaphoretic and laxative-like effects. Anti-rheumatic, antiseptic, and antipruritic activities have also been described, however the mechanism for these properties is undetermined. Some studies suggest that components of sarsaparilla bind to and help elicit the excretion of bacterial endotoxins (4,5,6).

Reported Uses

Sarsaparilla has been utilized to treat rheumatoid arthritis, kidney disease and gout. In naturopathic and herbal medicine, it is used mostly in combination with other herbs and is touted for its diaphoretic and blood/urino-genital ‘cleansing’ and detoxifying actions. The American Indians favored Jamaican Sarsaparilla as an antipyretic. The Mexican and Honduran varieties are used to treat gonorrhea, fevers, and GI disorders. Sarsaparilla has even been used to alleviate symptoms of leprosy and syphilis. A tea brew has been used topically for numerous skin conditions, including psoriasis, and ringworm. It is marketed to athletes as having similar effects as anabolic steroids, but without the associated side effects. Smilax purportedly helps increase testosterone and progesterone levels in the body, as well as stimulate the sexual organs. A recent (2001) U.S. patent was filed on sarsaparilla (*Smilax china*) for keratosis and respiratory diseases. At one time the root was used commercially as a foaming ingredient in root beer and other soft drinks (2,7).

Dosage

Sarsaparilla, increasingly available in health food stores, is found in variety of tablets, capsules, and tincture products. Typical dosages range from 1 to 4 grams of the dried root or 5 to 10 ml of a fluid extract daily. A cup of tea is another delivery route typically taken three times a day and prepared by boiling the dried root in water for 5 to 10 minutes and then straining the extract.

Scientific Evidence

Evidence is scarce to support the majority of the purported uses of Smilax. The sterols contained in sarsaparilla are the plant variety; they are not anabolic nor are they converted to anabolic steroids *in vivo*. Testosterone has never been detected in any plant, including sarsaparilla (4,6).

Sarsaponin, one of the plant sterols, has been found to bind to endotoxins in the serum, which may explain why the root has a long history as a blood “purifier”. Increased endotoxin levels are found in the blood of patients with psoriasis, and there is clinical evidence to

support improvement in the associated symptoms with the use of sarsaparilla (5,8,9). Other conditions associated with high endotoxin levels include eczema, arthritis, and ulcerative colitis. Again, this may possibly explain its long history of use in some of these diseases. Human trials have shown Smilax to be of some use for relieving symptoms of both leprosy and syphilis (10).

Sarsaparilla may improve the digestive process, and even increase appetite.

Although recent studies have focused on possible hepato-protective and anti-inflammatory effects, there is little conclusive data (5,11). A recent (2001) U.S. patent identified Smilax as having the ability to treat senile dementia, cognitive dysfunction, and Alzheimer's disease, as well as being a prophylactic and therapeutic medicine for numerous acute respiratory conditions. The observations reported in the patent have yet to be published in any peer-reviewed journals.

Adverse Reactions

GI: Mild gastric irritant; large doses may lead to gastrointestinal upset.

Other: Dust from the root can aggravate or induce an asthmatic response (12).

Drug Interactions

- Digoxin: can increase the absorption of Digitalis glycosides.
- May accelerate the elimination of hypnotic drugs from the body.
- Can theoretically increase the absorption and/or elimination of simultaneously administered drugs (3).

Contraindications

Large doses can lead to European cholera, diuresis, and shock (13). Patients with kidney disease or using drugs eliminated renally should avoid use of this product. Asthmatics should avoid exposure to the root dust.

Comments

AVOID CONFUSION WITH HEMIDESMUS INDICUS, AKA. INDIAN OR FALSE SARSAPARILLA, family Asclepiadaceae. This has none of the saponins or other principal constituents found in sarsaparilla.

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6. ZMA

Sources

ZMA is sold as a non-prescription supplement in capsule form under numerous names including BEV ZMA, Z-Mass, Z-Mass PM, Cyclo Z-Mass, and a multitude of other brand names, all containing the description 'ZMA'.

Chemical Composition

ZMA is a triad of zinc monomethionine and zinc aspartate, magnesium aspartate, and vitamin B-6 (pyridoxine). ZMA is an acronym for Zinc Magnesium Aspartate, which evolved from its original meaning, zinc monomethionine aspartate when the formula was modified to include magnesium aspartate and B-6 (1).

Mechanism of Action

General claims to the product's potential include increased free testosterone and Insulin Growth Factor levels. It is supposed to be helpful in obtaining a restful sleep, and maximizing anabolic performance changes while sleeping and during exercise, which should lead to increased muscle strength, increased endurance, healing, and growth. The magnesium is purported to activate enzymes necessary for the metabolism of CHOs and amino acids, while zinc is used for promoting healing, tissue repair, and muscle growth, and vitamin B-6 serves as a cofactor to further enhance uptake and utilization.

Reported Uses

ZMA is purported to provide anabolic support to improve muscle strength, endurance, and sleep quality, and to promote tissue repair and generalized healing. Often ZMA is advertised to replace losses of zinc and magnesium during exercise which could diminish performance.

Dosage

Usually sold in capsule form in varying quantities:

Magnesium (from magnesium aspartate): 150-450mg

Zinc (from zinc monomethionine and zinc aspartate): 20-30mg

Vitamin B6: 7-10.5mg

The product is taken orally once per day after dinner/prior to bedtime, with 3 capsules normally recommended for men and 2 for women.

Scientific Evidence

Numerous bodybuilding and supplement websites reference a study in which the founder of the product is an author. The study claims that ZMA may have been the cause of increased leg strength, testosterone, and Insulin-like Growth Factor-1 levels when compared to a placebo group in measurements of NCAA football players over an 8-week trial. However, the study is generally considered flawed given the low levels of zinc and magnesium measured in these players at the onset of the study. This is the only clinical trial of ZMA to date (2).

Zinc, Magnesium, and Vitamin B-6 are all considered essential nutrients and vital to a properly balanced diet. Each nutrient can be linked to hundreds of chemical processes, and as such, significant amounts of research as well as medically indicated uses have been documented for each of them. However few studies provide conclusive evidence pertaining to the effects of supplementation of these minerals above and beyond their respective Recommended Dietary

Allowance, together or alone, on performance or exercise parameters. Some general statements about magnesium and zinc can be made.

Whereas the diets of most peoples are sufficient to meet their nutrient needs, some evidence indicates that many athletes may have a zinc deficiency. In particular, women are at greater risk of a deficiency (3), in part because they eat less food than men. Zinc deficiencies are often found in endurance athletes who adopt a high CHO, low protein diet in an attempt to enhance performance, as well as in wrestlers and dancers whose body weight restrictions are integral to their performance (4,5,6,7). The effects of a severe zinc deficiency are well documented in animal studies: skeletal muscle performance and resistance to fatigue are both diminished, as well as decreased muscle growth (8,9,10)

Only a handful of studies have examined zinc supplementation in those whose zinc status is not compromised. Krotkiewski et al. (12) concluded that zinc may be beneficial for fast twitch muscle activities, and suggested the role of zinc as a cofactor for lactate dehydrogenase may explain the beneficial results. Another experiment with zinc supplementation and aerobic exercise performance found no benefit (13). More studies are clearly necessary to elucidate the role of supplementation of zinc for performance enhancement (14).

Dietary magnesium intake by most athletes appears to be adequate, particularly when compared to other minerals (5,15,16,17). However, significant quantities of magnesium can be lost during exercise via sweat and cellular exfoliation. Several animal and human studies have confirmed magnesium supplementation may be beneficial in terms of improved muscle function (after a strength training regimen), cardiopulmonary performance, and cellular metabolism, when magnesium status is already compromised. However, most research on magnesium supplementation have shown no improvement in short or long-term exercise performance as compared to controls. Most authors, as well as the American Dietetic Association, Dietitians of Canada, and the American College of Sports Medicine do not recommend supplementation unless the person's diet is in fact deficient (18).

Finally, limited evidence suggests an alteration in vitamin B-6 metabolism during strenuous exercise, but exercise does not appear to increase B-6 requirements in animals. Some authors suggest that physically active people are at an increased risk of vitamin B6 deficiency (19-21). Despite the evidence for zinc, magnesium and B-6, these nutrients have not been carefully studied as a unit, the way ZMA is marketed. More research is necessary.

Adverse Reactions

The safety of ZMA as a unit is unknown.

Zinc: Chronically high intakes of zinc ((450-1600mg) daily can cause sideroblastic anemia, induce a copper deficiency, and impair immune function. Overdosing may cause diarrhea, vomiting, flu-like symptoms, GI tract upset, acute tubular necrosis, and interstitial nephritis. Zinc is likely safe for use in pregnancy and lactation if the upper intake levels are not exceeded. Higher doses have been associated with premature births and stillbirths in the third trimester, and copper deficiency in breast fed infants. There are no reported side effects for the zinc quantities found in ZMA if taken as recommended. (25,26)

Magnesium: Oral doses greater than 350mg per day may cause watery diarrhea. Hypotension, nausea, vomiting, mental status changes, loss of deep tendon reflexes, respiratory depression, cardiac arrhythmias and death are associated with a hypermagnesemic state. Such side effects are typically associated with parental administration. Magnesium supplementation is likely safe in pregnancy and lactation only in doses below 350 mg per day. The doses most often

recommended for taking ZMA may result in diarrhea, but are unlikely to cause more significant adverse effects

Vitamin B6: High doses have been associated with nausea, vomiting, abdominal pain, and headaches, among other side effects. More than 200 mg per day can cause a sensory peripheral neuropathy. Vitamin B6 is likely safe for use in pregnancy when taken as recommended. High dose pyridoxine may cause neonatal seizures. If the recommended doses found in ZMA are taken on a long-term basis, ulcerative colitis may be an issue. Otherwise the quantity is likely safe for regular use. (29,30)

Drug Interactions

No specific interactions with ZMA are identified in the literature. The potential drug interactions with its individual constituents are too numerous to identify in this forum. As with any drug, other medications should be evaluated for potential interactions with regard to adverse outcomes in combination with this product.

Comments

None

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7. Ecdysterone (20-Beta-Hydroxyecdysterone)

Sources

Alfa-ecdysone, Beta-ecdysone, Ecdisten, Ecdysone, Hydroxyecdysterone, Isoinokosterone Syntrax Syntrabol, ECDY-20™

Chemical Composition

Ecdysterone, or 20-Beta-Hydroxyecdysterone, is a chemical found in insects, some marine invertebrates, and some plants. Technical names include ecdisten, ecdysone, isoinokosterone, 20-hydroxyecdysone and β-ecdysterone.

Mechanisms of Action

Ecdysterone has a structure similar to testosterone, and may have anabolic properties. Animal research suggests that ecdysterone affects steroid receptors, but it is unclear whether this effect is mediated by regulation of the receptor, changes in feedback sensitivity, or by bioconversion into steroids. Another potential mechanism includes anticatabolic effects by blocking cortisol receptors.

Reported Uses

Ecdysterone is used primarily to increase muscle mass and strength, enhance protein accretion, and accentuate muscle definition.

Dosage

The typical dosage recommended by various manufacturers is 80 to 600 mg per day or 5 mg/kg body weight.

Scientific Evidence

No scientific reports are available in mainstream literature. However, there are websites (<http://www.bodybuilding.com/store/ecdy.html>) promoting literature in other languages from other countries, all of which indicate very positive findings. A list of references from the Russian and Chinese literature is provided below, but most of these studies are difficult to find or have not been translated. Clearly, ecdysterone and its analogs have been of interest for a long time (since at least 1976) for a variety of reasons, including insulin sensitivity and erythropoiesis. It is also difficult to assess the integrity of the studies without access to them. Even then, the translations and results are questionable.

Adverse Reactions

None reported.

Drug Interactions

None known.

Contraindications

None known.

Comments

This new supplement should be watched carefully as little is known about it and manufacturers are likely to promote products containing ecdysterone that are contaminated. This is because of where it is derived naturally. It is often used in conjunction with methoxy and ipriflavone, other agents being touted as anabolic in nature.

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8. Methoxyisoflavone (5-Methyl-7-methoxyisoflavone) and Ipriflavone (7-isopropoxyisoflavone)

Sources

IpriBone, Ipurosa, Iberogast, Iberis coronaria, MethOxyvone, Androbolic, HCG Trans Testicular, Methoxy-7, and TRIBOLAN™, Cytodyne Methoxy-Pro Protein Powder, IsoDyne

Chemical Composition

Methoxyisoflavone (5-Methyl-7-methoxyisoflavone) and Ipriflavone (7-isopropoxyisoflavone) are powerful anabolic isoflavones similar to those found in soy

Sources

Both of these products, called “isoflavones”, are a subclass of phytoestrogen and a group of polyphenolic plant compounds. Isoflavones are found almost exclusively in legumes, or pulses, to include lentils, clover, chickpeas and a large variety of beans. Soybeans are the most abundant source of isoflavones, and as such, soy foods are the major dietary source of these bioactive non-nutrients. Many different isoflavones are also being synthesized, but food sources are the best.

Mechanism of Action

In the context of osteoporosis and bone metabolism, ipriflavone is considered to exert both anti-resorptive and bone-forming action(1,2). It is anti-resorptive by inhibiting parathyroid hormone-, vitamin D-, PGE2- and interleukin 1 β -stimulated bone resorption (1), whereas it may also regulate osteoblastic differentiation by enhancing the expression of important bone-matrix proteins and facilitating mineralization (2).

The anabolic mechanisms for methoxyisoflavone and ipriflavone in combination is less clear, but mechanisms suggested include reducing cortisol and estrogen levels, and increasing protein synthesis and nitrogen retention.

Reported Uses

With respect to performance enhancement, ipriflavone and methoxyisoflavone are used in combination with the expectation of increasing protein synthesis, improving recovery after strenuous exercise, increasing muscle mass, and reducing body fat. However, the most widespread use of ipriflavone is for preventing and treating postmenopausal and senile osteoporosis, preventing drug-induced osteoporosis, relieving osteoporotic pain, treating Paget's disease and renal osteodystrophy, and for reducing bone loss in hemiplegic stroke patients.

Dosages

Methoxyisoflavone (5-methyl-7-methoxyisoflavone): 25 -150 mg each day

Ipriflavone (7-isopropoxyisoflavone): 40 - 50 mg each day

Scientific Evidence

A multitude of studies have been conducted to assess the effects of ipriflavone on the treatment of osteoporosis or low bone mass in postmenopausal women. Ipriflavone plus calcium 1000 mg daily appears to be able to prevent further loss of bone mineral density (BMD) in postmenopausal women with osteoporosis or low bone mass (3-5). There is some evidence that it can actually increase BMD in some patients (6). However, negative results were found in a prospective, randomized, double blind, placebo-controlled, 4-year study conducted in four centers in Belgium, Denmark, and Italy of 474 postmenopausal white women, aged 45 to 75 years, with bone mineral densities (BMDs) of less than 0.86 g/cm (7). The women were randomly assigned to receive ipriflavone, 200 mg 3 times per day (n = 234), or placebo (n = 240), and all received 500 mg/d of calcium. No benefit was found with ipriflavone. For this reason, a recent report from Canada (8) did not include ipriflavone in the recommendations for osteoporosis. However, it seems that low dose estrogen plus ipriflavone seem to maintain or increase BMD in postmenopausal women better than either agent alone (9).

Other studies have shown that ipriflavone can also significantly reduce osteoporotic pain and may actually be as effective as inhaled calcitonin (4,10). Furthermore, ipriflavone may be of use as a therapeutic agent against osteolytic bone metastasis (1) and glucocorticoid-induced osteoporosis (11). Overall, ipriflavone is of great interest with respect to osteoporosis and deserves further study (13-16).

The use of ipriflavone and methoxyisoflavone for anabolic actions is not documented in mainstream literature, but it is touted as a benefit on the internet by manufacturers trying to sell a product.

Adverse Reactions

CNS: Dizziness

GI: Epigastric pain, diarrhea

Hematologic:Subclinical lymphocytopenia if taken for greater than 6 months

Drug Interactions

- Calcitonin: potential for ipriflavone to enhance effects of calcitonin on relieving bone pain in patients with osteoporosis.
- Estrogen: Ipriflavone seems to have additive effects on BMD and bone resorption when used in combination with estrogen.
- Concomitant use can increase serum theophylline levels.
- Ipriflavone is thought to competitively inhibit cytochrome P450 1A2 and 2C9

Contraindications

Should not be used if pregnant or lactating due to insufficient data.

Comments

Appears to be an interesting group of substances.

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9. Designer Steroids

Sources

Designer steroids, specific forms of synthetic anabolic steroids, are unique in that they may not show up in drug testing. Synthetic steroids are obtained as a prescription drug therapy, illegal purchases, or as a pre-cursor form in various supplements. The most recent designer steroid, called Tetrahydrogestrinone, or THG, has become a drug of controversy in many professional sports (1). Two other steroids that are being scrutinized are 1-testosterone or 4-hydroxy-testosterone. Although only steroid precursors, they are thought to be the equivalent of designer steroids, and can be purchased at health food stores or online at most bodybuilding websites (2). There are numerous other steroid pre-cursors sold in supplements, such as 1-Test, 1-TestEther, atomic T-Bol, One, T-100, TestXtreme, Androgen-1, Testosterol XP, TestXtreme, and Mag10 (3).

Chemical Composition

Anabolic steroids are artificially produced hormones similar to the male sex hormones (1). These forms of steroids, including anabolic and androgenic, liquid and pill, are all slightly different but resemble the hormone testosterone. Although similar to the steroids originating naturally in the human body, synthetic hormones and steroids can be much more potent. The most recent designer steroid, THG, has been identified as the drug tetrahydrogestrinone, which is a modification of two well-known synthetic, and illegal steroids: trenbolone and gestrinone.

Mechanism of Action

Anabolic steroids mimic the effect of testosterone, which stimulates growth of muscle tissue. Designer Steroids are manufactured specifically to bypass drug tests, so they are made without known drug signatures. The tests currently used to detect anabolic steroids and other drugs rely on established drug signatures, or breakdown products, that show up in tests. Without such signatures a drug cannot be detected.

Reported Uses

Steroids have become popular as they improve endurance, strength, and muscle mass. Designer steroids are mainly used by professional athletes and competitors who need to bypass drug tests. Companies thought to be selling THG have marketed their products to athletes in track and field, players in the NBA, NFL, Major League Baseball, and professional tennis athletes (4). In a related market, designer steroids are being sold in dietary supplements because they come from "natural sources". People taking these dietary supplements may not be fully aware of exactly what substances they are ingesting (4).

Steroids can be sold legally by a prescription for treatment purposes only. They are commonly used to treat conditions in which the body produces abnormally low amounts of testosterone. Steroids can also be used for treatment of persons with AIDS or other diseases that result in loss of lean muscle mass (1).

Dosages

Steroids can be taken orally or injected, typically in cycles of weeks or months (1). Specific doses of designer steroids are dependent upon the type and purpose of the steroid being taken. It is well known that many people taking steroids for non-treatment purposes tend to consume higher dosages than would be medically recommended.

Scientific Evidence

Some animal studies have been conducted to examine the effect of designer steroids on liver function and tissue growth, whereas human studies have focused on possible psychiatric effects of synthetic steroid use (3). What is very clear is that such steroids confer performance benefits, but at an incredible price.

The American College of Sports Medicine (ACSM) was outraged at the promotion of such drugs, as they are considered to be for the sake of deceiving the athletic community. The recently identified THG, which was developed and cloaked to avoid detection by doping tests, are serious threats to the health and safety of athletes, as well as detriments to the principle of fair play in sports. Any effort to veil or disguise steroid use in sports through stealth, design, or precursor changes, puts elite, amateur and even recreational athletes at risk.

Adverse Reactions

CNS: Mood swings and aggression

CV: Fluid retention, high blood pressure, increased risk of heart disease, increases in LDL, decreased HDL

GU: Shrinking of the testicles, reduced sperm count, infertility, changes in or cessation of the menstrual cycle, enlargement of the clitoris and breasts

Musculoskeletal: premature closure of growth plates, increase in tendon injuries

Skin: Acne, purple or red spots on the body, facial hair for women

Other: Liver tumors and cancer, jaundice, kidney tumors, swelling of legs and feet, an increased risk for prostate cancer, baldness

Drug Interactions

Unknown

Contraindications

Steroids are contraindicated in women who are or may become pregnant. Also people with systemic hypertension, congestive heart failure, diabetes, osteoporosis and stomach ulcers should not take steroids. Children are also advised not to take steroids as it can affect normal growth.

Comments

Steroids are illegal in the United States unless prescribed by a doctor. Therefore, using them for bodybuilding, recreational or athletic reasons is not allowed. Because of it's illegality, there have been many controversies with professional athletes using illegal steroids. The ACSM called for mandatory testing for steroid use in Major League Baseball. They also have a written Position Stand, "The Use of Anabolic-Androgenic Steroids in Sports" in which the use of these drugs among athletes was condemned. A copy of this Position Stand can be found at <http://www.acsm-msse.org>). Unfortunately, information compiled over just the past few years, indicates an upward trend in steroid use among amateur athletes at the college and even high school levels. Please also refer to Comments under Androstenedione regarding The Anabolic Steroid Control Act of 2003.

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October 17th, 2003.

10. Yohimbine

Sources

Yohimbe comes from the bark of an evergreen tree native to Zaire, Cameroon, and Gabon. The tree bark contains the active compound, yohimbine. It is also found in the South American herb, Quebracho (*Aspidosperma quebracho-blanco*). A purified extract from yohimbe bark yields an alkaloid (stimulant similar to caffeine and ephedra) called Yohimbine, which is regulated as a prescription medication and used for treating erectile dysfunction in males. This substance is also promoted as a male aphrodisiac and a natural form of Viagra. Common names are Yohimbe-Plus, Yohime Bark, and Yohimbe Extract.

Chemical Composition

An alkaloid (stimulant similar to caffeine and ephedra) called Yohimbine is extracted and purified from yohimbe bark. Yohimbine is regulated as a prescription medication and used for treating erectile dysfunction in males.

Mechanisms of Action

Yohimbe functions as a monoamine oxidase (MAO) inhibitor to increase levels of the neurotransmitter, norepinephrine. Yohimbine also acts as a central nervous system stimulator, where it blocks specific receptors (α -2 adrenergic receptors). Yohimbe can also dilate blood vessels.

Reported Uses

Yohimbe has traditionally been used as a stimulant and aphrodisiac in West Africa and South America. In the United States, yohimbe and quebracho are most often promoted in dietary supplements as effective in increasing muscle mass by boosting testosterone levels, accelerating weight loss, increasing energy levels, enhancing sexual performance (aphrodisiac and erectile function), and relieving depression. It is often marketed as "herbal Viagra" and as an alternative to anabolic steroids.

Dosage

Typical daily amounts of yohimbine alkaloids found in commercial supplements (label claims) are often in the range of 10-30 mg and occasionally standardized to yohimbine or total alkaloid content. More than 40 mg/day of yohimbine can result in adverse side effects.

Scientific Evidence

Yohimbe is promoted as a "natural" way to increase testosterone levels and build muscle, increase strength and lose fat, but there is no solid scientific proof that yohimbe is either anabolic or thermogenic (1). Several small studies indicate that yohimbine can increase blood flow to the genitals and thereby alleviate some mild forms of both "psychological" and "physical" impotence. Overall, yohimbe does appear to have a modest therapeutic benefit over placebo, particularly in essentially psychogenic erectile disorder, and is generally well tolerated (2,3,4,5,6).

Adverse Reactions

CNS: Hallucinations, tremors, insomnia, anxiety, dizziness, headache

CV: Hypertension, tachycardia, heart palpitations

GI: Gastric intolerance, nausea, vomiting
GU: Urinary frequency,
Skin: Rashes, itchy/scaly skin
Other: Salivation, sinusitis, irritability, fluid retention

Drug Interactions

- α -2-Adrenergic Blockers: Yohimbe may enhance activity of such drugs.
- Anti-diabetic drugs: Yohimbe can interfere because of MAO activity.
- Anti-hypertensive Agents: Can interfere with blood pressure control.
- β -Blockers: Should minimize yohimbine toxicity.
- Clondine/Catapres and Guanabenz: Yohimbine may antagonize intended drug effects.
- MAOIs: Concomitant use with yohimbe can result in additive effects.
- Naloxone/Narcan: Concomitant use can have additive therapeutic and adverse effects.
- Phenothiazines: Contraindicated because of increased α -2-Adrenergic antagonism.
- Sympathomimetic Agents: Yohimbe is contraindicated because increases the risk of hypertensive crisis due to MAO inhibitor activity.
- Tricyclic Antidepressants: Contraindicated due to potential to increase or decrease blood pressure.

Contraindications

People with high blood pressure and kidney disease should avoid supplements containing yohimbe as should women who are (or who could become) pregnant due to abortion risk. Also, caution should be used with yohimbe taken in combination with certain foods containing tyramine (red wine, liver, and cheese) as well as with nasal decongestants or diet aids with ephedrine or phenylpropanolamine (which could lead to blood pressure fluctuations). Occasionally, yohimbe is combined with serotonergic supplements (such as St. John's wort or 5-HTP) to increase their effectiveness. It is not recommended to combine yohimbe with other antidepressant supplements or medications except under the advice and supervision of a nutritionally-oriented physician.

Comments

Because yohimbine has such a powerful effect on blood pressure, large amounts of tyramine-containing foods (aged cheeses, fermented meats, red wines, and others) and vassopressor-containing foods (overripe fava beans, coffee, tea, colas, and chocolate) should be avoided.

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D. Protein and Amino Acids Products

1. Branched Chain Amino Acids: Leucine, Isoleucine, Valine

Sources

Eclipse 2000 Deluxe BCAA, Optimum BCAA 5000, SportPharma BCAA, Ultimate Nutrition Branch Chain Amino Acids, Ultimate Nutrition Mass Branch Chain Amino Acids, Hi-Test Muscle Octane BCAAs, and Hard Body BCAA. BCAAs are found in dietary protein, such as meat, dairy products, and legumes and can account for 15-25% of the total daily intake of protein (1,2).

Chemical Composition

Branched-chain amino acids (BCAA) are three essential amino acids that include leucine, isoleucine, and valine. They are also known by their scientific names of 2-amino-4-methylvaleric acid, 2-Amino-3-methylvaleric acid, and 2-Amino-3-methylbutyric acid respectively (1).

Mechanisms of Action

BCAAs are essential amino acids that act as modulators of protein synthesis, substrates for protein synthesis, and as precursors in the synthesis of alanine and glutamine. Leucine is the BCAA thought to be most responsible for stimulating protein synthesis. It does this by stimulating pancreatic islet cells to release insulin, which is required to maximally stimulate protein synthesis. BCAAs primarily stimulate protein synthesis in skeletal muscle and to a lesser extent adipose tissue and the liver (1-4).

The theory behind supplementing with BCAAs during exercise to prevent central fatigue is that the synthesis of serotonin is accelerated when blood levels of BCAA are low accelerate, and increased serotonin will lead to feelings of sleepiness and fatigue. Tryptophan, a precursor for serotonin, is more easily transported into the brain when BCAA levels are low. Thus, increasing blood levels of BCAA should block tryptophan transport into the brain and decrease serotonin production (1-4).

Reported Uses

BCAAs have been marketed by both the supplement industry and medical community for a number of uses (1-17). The supplement industry claims that BCAAs increase endurance and energy levels, prevent fatigue, improve mental performance, and decrease muscle breakdown during intense exercise (1-4). The medical community has looked at BCAAs in the treatment of amyotrophic lateral sclerosis (ALS), latent portosystemic encephalopathy, chronic hepatic encephalopathy, acute hepatic encephalopathy, mania, anorexia, and to attenuate muscle wasting during prolonged bed rest (5-10).

Dosage

Oral: Most supplement preparations range from 1-5 grams 2-3 times per day varying the quantity of the individual amino acids (2). It can also be added to a CHO containing beverage by using 1 to 7 grams of BCAA per liter of fluid (4).

For latent or chronic encephalopathy, a dose of 240 mg/kg/day have been used, with up to 25 grams per day. For decreasing the acute symptoms of mania, a 60 gram BCAA drink containing valine, isoleucine, and leucine in a ratio of 3:3:4 has been used for 7 consecutive mornings (1). Elderly patients on hemodialysis were given 12 grams per day for anorexia (5).

Intravenous: Standard solutions of amino acids that contain BCAAs are used for all forms of hepatic encephalopathy. The dosage ranges from 80-120 grams per day which provides approximately 28-43 grams of BCAAs (1).

Scientific Evidence

The uses of BCAAs for improving athletic performance and/or delaying fatigue have been well studied, and the results are not always supportive. Recent studies show no improvement in acute physical performance (11-13). However, one study demonstrated that BCAAs, when used orally, were effective in reducing muscle breakdown during exercise (14). In contrast, BCAA were ineffective for enhancing exercise or athletic performance (12).

Other than exercise, BCAA have some clear benefits. Administration of a BCAA beverage appears to diminish manic symptoms within 6 hours after ingestion and continues to ameliorate symptoms over the course of taking the beverage for seven days (5). Similarly, BCAA have been shown to be somewhat effective when used orally to reduce anorexia and improve the overall nutritional status by rapidly improving appetite and caloric intake, and increasing plasma albumin levels (7,8,9). Such preparations may also be useful for all forms of hepatic encephalopathy (9). Marchesini et al. (9) showed that oral BCAA supplementation was useful in preventing progressive hepatic failure and improved perceived health status in patients with advanced cirrhosis. However, there may have been compliance issues with these patients (9).

Finally, it may be that BCAA are not the answer, but rather that one of the specific amino acids is more important than another. In a review, Mero (12) concluded that BCAA supplementation (76% leucine) in combination with moderate energy restriction induced significant and preferential losses of visceral adipose tissue without a decrement in performance. However it was emphasized that interpreting the limited number of BCAA studies must be done with caution, since the proportion of leucine in the BCAA mixture may be critical. Consequently, further research into the effects of leucine supplementation alone is needed.

Adverse Reactions

CNS: Encephalopathy

Musculoskeletal: Loss of motor coordination

Other: Increased plasma ammonia, fatigue

Drug Interactions

- Levodopa: May compete for transports systems in gastrointestinal system and brain and decrease the effectiveness.
- Insulin: BCAAs may increase the release of insulin and have an additive effect with anti-diabetic drugs to cause hypoglycemia (1).

Contraindications

People with rare inborn errors of metabolism of maple syrup urine disease and isovaleric academia should not take BCAAs. One recent study indicates ALS patients should not use BCAAs (17).

Comments

BCAAs have a very sound theoretical base, but the scientific studies have not supported the theories.

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2. Whey Protein

Sources

Whey protein constitutes approximately 20% of the total protein found in milk. Numerous whey protein powder, concentrate, and isolate supplements are commercially available (1-4). Some of the products available include: WheyFit 2000, Super Whey Fuel, Triple Whey Fuel, Instant Soy'n Whey, and Nitro Fuel.

Chemical Composition

Whey protein is a co-product of cheese and casein manufacturing and contains about 12% of protein as a solid basis. Whey proteins, which are compact globular proteins, are universally defined as those proteins that remain in milk serum after coagulation of the caseins at pH 4.6 and 20°C. Whey contains lactose, calcium, sodium, phosphorus, potassium, alpha-lactalbumin, beta-lactoglobulin, lactoferrin, serum albumin, lysozyme, gamma-glutamylcysteine, and immunoglobulins A, G, and M. The protein in whey is typically about 24% BCAA (leucine, isoleucine, and valine) (1). The composition of the particular whey protein depends on how the product was processed and purified. It can exist as simple whey powder (30% or less total protein content), whey protein concentrate (30-85% protein) or whey protein isolate (90% or higher protein content) (2).

Mechanisms of Action

Protein is the primary macromolecule involved in growth, development and repair of all tissues in the body. During exercise, the human body is in a catabolic state followed by an anabolic state after terminating the exercise. It is postulated that providing essential amino acids can shift the balance between catabolism and anabolism during this recovery phase. The proteins

found in whey are of a high quality and contain a high percent of BCAAs, with leucine serving a major role in regulating protein metabolism. Leucine may serve as a key signal in muscle protein synthesis through intracellular signaling pathways (4). The amino acid profile of whey protein is very similar to the amino acid composition of human skeletal muscle.

Whey may also affect body composition by decreasing fat stores and enhancing satiety. The mechanism by which whey is responsible for decreasing fat stores has not been shown directly, but it may be by suppressing calcitrophic hormones through maintenance of high serum calcium levels, which serves to inhibit lipogenesis and stimulate lipolysis (4). The mechanism of early satiety by certain whey peptides is not fully understood. One recent study implicated post-absorptive increases in plasma amino acids together with increases of both serum cholecystokinin and glucagon-like peptide 1 as potential mediators (5).

Whey protein is a source of gamma-glutamylcysteine, a precursor of glutathione (GSH) that acts as an intracellular antioxidant. Ingestion of whey protein may maintain GSH levels and benefit a number of conditions in which GSH is depleted, such as infections, trauma, and surgery. Lastly, whey protein contain immunoglobulins, which are thought to bind antigens in the gut and prevent their absorption (1,4).

Reported Uses

Protein supplementation is used by athletes to promote positive nitrogen balance throughout the day without dramatically increasing caloric intake. Specifically, it is reported that whey protein may help build muscles, increase strength, control appetite, aid in weight loss, improve endurance, and boost energy levels. It is also used in cancer prevention and treatment, to reverse weight loss, increase GSH, and enhance immune function (1,2).

Dosage

Protein intake varies depending upon activity level and types of activities. The recommended daily protein intake for people with sedentary lifestyles is 0.8g/kg of body weight. The recommended daily protein intake for strength athletes is 1.7-1.8 g/kg of body weight. The recommended daily intake of protein for endurance athletes is 1.2-1.4 g/kg of body weight (3). Whey protein supplementation alone ranges from 20 to 84 g/day.

Scientific Evidence

Multiple studies of whey protein and exercise have been conducted, but in many, whey protein was used as the control and compared against colostrum protein (4-7). Whey protein seems to be of use, but no clear benefit was noted. In contrast, Burke et al. (8) studied the effects of resistance training and whey protein supplementation with and without creatine monohydrate supplementation on lean tissue mass and muscle strength, and concluded supplementation with whey protein and training resulted in greater improvements in knee extension peak torque and lean tissue mass than training alone. However, supplementation with whey protein and creatine yielded greater increases in lean tissue mass and bench press than only whey protein or placebo.

One of the issues with high protein diets is kidney function (9,10,11). Poortmans et al. (9) studied the effects of high protein diets on kidney function in body-builders and other well-trained athletes and concluded that a protein intake under 2.8 g/kg/d does not impair renal function in well-trained athletes (9).

With respect to benefits other than athletics, whey protein can be important. It has been shown to be effective when used as a replacement for, or in addition to, milk-based infant formulas (12). Likewise, whey protein may contain agents that assist with satiety (13), may be

important when trying to maintain nutritional status and GSH levels of people with HIV disease (14) and in treating metastatic carcinoma (15).

Adverse Reactions

CNS: Fatigue, and headache

GI: Increased stool frequency, nausea, bloating, cramps, reduced appetite

Other: Renal function, increase BUN, thirst.

Drug Interactions

No known drug interactions.

- Could decrease absorption of alendronate, fluoroquinolones, levodopa, and tetracyclines (1).

Contraindications

People who are lactose intolerant should not consume whey products.

Comments

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3. Colostrum Protein

Sources

Colostrum is the clear to cloudy fluid secreted by mammary glands prior to full lactation. For supplement use, the main supply is from cattle. Commercial products include NitroSyn Protein, HUMATROP, Bulk Factors, Ghboost, Colostrum, Primo HGH Stak, Gro Tropin, Infusion, MegaTropin, Animal Pak!, Bovine Colostrum, Hyperimmune Bovine Colostrum, Bioenergie, Dynamic, and Intact.

Chemical Composition

Colostrum contains a variety of substances including immunoglobulins, proline-rich polypeptides, lactoferrin, glycoproteins, lactalbumins, cytokines, lysozymes, growth factors, and vitamins and minerals. Hyperimmune colostrum is derived from cattle immunized against specific pathogens, which results in increased antibody titers against those pathogens (1).

Mechanisms of Action

The variety of substances in colostrum makes the mechanism of action complex (1-4). The immunoglobulins found in colostrum are responsible for the anti-diarrheal effects. Although the concentration of immunoglobulins in bovine colostrum is too low to be effective against pathogens, cows sensitized against specific pathogens have increased concentrations of immunoglobulins and hyperimmune colostrum may provide immunoglobulins to fight enteric pathogens. Bovine colostrum also contains growth factors that may be responsible for increased athletic performance. One such factor is insulin-like growth factor 1 (IGF-1). Other growth factors and cytokines within colostrum are thought to be responsible for enhanced protection and repair capability of the gastrointestinal (GI) tract.

Reported Use

Bovine colostrum is used orally to aid in athletic performance and sculpt body composition by increasing lean mass. Other uses include support for and stimulation of immune system function, GI protection and healing. Specifically, colostrum or hyperimmune colostrum has been used as protection against NSAID damage to GI tract, decreasing diarrhea associated with certain strains of *E. coli*, HIV, rotavirus infections in children, and graft versus host disease. Bovine colostrum has also been used rectally to treat left-sided colitis.

Dosage

Oral: for athletic performance: 25 ml or 125 ml colostrum suspension or 20 or 60 grams in powder form has been used. For various types of diarrhea, 10 to 20 grams in powder form, have been used up to four times per day for 10 to 21 consecutive days.

Rectal: A 100 ml 10% solution colostrum enema has been used in the treatment of left-sided colitis (17).

Scientific Evidence

Many studies have been conducted testing the efficacy of colostrum on enhancing athletic performance with mixed results (5-13). Several studies have been conducted testing whether supplementation with colostrum increases serum insulin-like growth factor I (IGF-I), which is one of the proposed mechanisms for enhancing athletic performance (5-8). An initial study by Mero et al. (5) and then a follow-up study (6) looked at serum IGF-I levels in athletes following supplementation with two different forms of colostrum. They concluded that supplementation with oral bovine colostrum increased levels IGF-I and that the increase was not from directly absorbing the IGF-I from the colostrum (6). Kuipers et al. (7) and Buckley et al. (8) measured the effect of colostrum supplementation on serum IGF-I levels and found no change in

athletes following supplementation (7,8). Other investigators looked directly at the effects of colostrum supplementation on athletic performance, again with some mixed results. Buckley et al. (8) looked at supplementation during endurance running and Hoffman et al. (9) on performance of elite field hockey players: neither found any endurance performance benefit, but Buckley et al. (8) found an improvement in recovery time and Hoffman et al. (9) noted improvement in sprint performance. Brinkworth et al. (10) found no improvement in performance for elite female rowers, but an enhanced buffering capacity was noted (10). In another study, Coombes et al. (11) found that colostrum supplementation resulted in a small but significant improvement in time trial performance of cyclists after a 2-h ride at 65% their maximal aerobic capacity. Finally, Antonio et al. (12) compared colostrum and whey protein supplementation in active men and women, in the amount of 20 grams/day in combination with aerobic and heavy-resistance training at least three times per week for eight weeks. They reported that colostrum resulted in an increase in bone-free lean body mass, whereas only weight was gained with the whey protein. It would seem that much research remains regarding the effects of colostrum on physical performance and body composition.

Colostrum is also used for many other purposes, including the prevention of NSAID injury to the gastrointestinal mucosa (13,14). Playford et al. (13,14) studied the efficacy of colostrum supplementation in the prevention of NSAID injury to the gastrointestinal mucosa in animal models and humans respectively and concluded that colostrum could help protect against NSAID-induced GI injury (13,14). Others have evaluated the efficacy of colostrum for treating diarrhea (15-19). The reports indicate that children with various forms of diarrhea who received immunized bovine colostrum had significantly less daily and total stool output and stool frequency (15,16). Similarly, several investigators have found that oral bovine colostrum is effective in the treatment of diarrhea in HIV patients (17-19). Finally, Khan et al. (20) found colostrum enema treatments to be effective when treating patients with left-side colitis. In summary, colostrum is a very interesting product with many potential benefits.

Adverse Reactions

Few adverse reactions have been reported.

GI: Nausea and vomiting

Other: Potential for allergic reactions in patients who have bovine milk allergies.

Drug Interactions

There are none known at this time.

Contraindications

People with allergies to bovine milk products should not use this product.

Comments

Bovine colostrum could provide a novel, inexpensive approach for the prevention and treatment of the injurious effects of NSAIDs on the gut and may also be of value for the treatment of other ulcerative conditions of the bowel (13,14).

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4. Casein Sources

Casein, a protein derived from milk products, is found in several forms including calcium caseinate, sodium caseinate, acid casein, rennet casein, and micellar casein (1-3). Micellar casein is the form most often sold as a dietary supplement. Some popular micellar casein products include Cytosport Muscle Milk, VPX Micellean, Syntrex Isomatrix, Prolab Mean Mass Matrix, and EAS Myoplex Deluxe (1-4).

Chemical Composition

Casein is the dominant protein in bovine milk. Micellar casein, the undenatured form of casein, is composed of proteins configured in a micellar conformation. Casein is generally

defined as the protein precipitated at pH 4.6, whereas whey protein are those proteins that remain in milk serum after coagulation of the caseins. Casein can be separated electrophoretically into four major components: alpha-casein, beta-casein, gamma-casein, and kappa-casein. Casein is made from nine essential and nine non-essential amino acids (1-4).

Mechanisms of Action

Casein, provides all of the amino acids necessary for growth. Unlike other protein supplements, casein protein forms a gel in the stomach, which allows it to be digested more slowly so the peptides/amino acids are absorbed steadily over a long period of time, unlike whey protein, which is absorbed very quickly. Some studies have shown that a slowly digested protein may increase endogenous protein synthesis and suppress endogenous protein breakdown. In other words, a slow digesting protein following strenuous exercise may ensure a steady supply and release of amino acid, which could potentially accelerate repair and regeneration of damaged tissues (2,3).

Reported Uses

Protein supplementation is used primarily by athletes to increase muscle mass and strength, control appetite, aid in weight loss, improve endurance, boost energy levels and promote immune function (1-4).

Dosage

Protein intake varies depending upon activity level and types of activities. The recommended daily protein intake for people with sedentary lifestyles is 0.8g/kg of body weight. The recommended daily protein intake for strength athletes is 1.7-1.8 g/kg of body weight whereas the recommended intake for endurance athletes is 1.2-1.4 g/kg of body weight.

Scientific Evidence

A body of evidence regarding casein and protein synthesis/accretion exists. However, a controversy between casein and whey protein has arisen and is quite interesting. There are two schools of thought - one that recognizes only the importance of whey and the other casein. In fact, both are important, and demonstrate why whole foods are better than supplements. Dangin et al. (5-7) evaluated how the rate of protein digestion and metabolism (casein protein to whey protein) differed across age populations: young and elderly. They reported that elderly patients had better protein retention when supplementing with whey protein, whereas young persons had better protein retention when taking casein products. They concluded that a “fast” protein such as whey would be better than a “slow” protein, such as casein in the aging population (6,7). One way to look at the issue is to recognize that whey and casein have different benefits and accept the fact that the best protein source is a mixed protein source. Whey is a great choice if the protein is consumed regularly, like every two hours, whereas casein is preferred if the protein is taken every six hours.

The literature indicate that slowly digested proteins (casein) induce a higher protein gain in young men than rapidly digested protein (whey). Boirie et al. (5) and Dangin et al. (5,6,7) compared the rate of protein digestion on postprandial anabolism of protein and the effects of casein to those of whey protein on whole body metabolism of protein in young people. In both studies, whey protein induced a dramatic but short term increase in plasma amino acids, while casein protein resulted in a prolonged increase in plasma amino acid levels. The overall conclusions were that the rate of protein digestion was an independent factor in regulating whole body protein metabolism (5-7). However, when they conducted these studies in older men, a

different pattern was noted: protein gains appeared to be greater during aging with rapidly digested proteins as compared to slowly digested protein (8).

Other issues must also be considered, Demling et al. (9) studied the interactions between 12 weeks on a hypocaloric diet in combination with increased whey protein or casein protein (1.5 g/kg/day) and a resistance training program on lean mass gains and fat mass loss in overweight police officers. Weight loss was similar in all three groups but percent body fat loss and lean mass gains and increases in chest, shoulder, and leg strength were greatest in the casein supplemented group. They concluded that the significant differences in body composition and strength were due to improved nitrogen retention and anabolic effects caused by the peptide components of the casein hydrolysate (9). Whether these results would have been obtained if a isocaloric diet had been provided is unknown. Regardless, the data indicate that protein is important, and that high quality proteins are essential, but that other specific protein characteristics may not be an issue.

Adverse Reactions

None to date.

Drug Interactions

No known drug interactions are known.

Contraindications

People who are lactose intolerant should not consume casein products.

Comments

The entire issue of protein supplementation has been going on for many years without closure. The truth remains to be uncovered.

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E. Miscellaneous

1. Melatonin

Sources

Melatonin is synthesized and secreted by the pineal gland with daily and seasonal rhythms. These rhythms are controlled by the circadian oscillator located in the hypothalamus (1-3). Melatonin is also synthesized in the retina, Harderian gland, gut mucosa, cerebellum, airway epithelium, liver, kidney, adrenals, thymus, thyroid, pancreas, ovary, carotid body, placenta and endometrium (4). It can also be bought over-the-counter in either synthetic or natural forms. “Higher Power Melatonin” “Nature’s Science Melatonin” and “Twinlab Melatonin” all are 100% pure melatonin products. However, melatonin can also be found in more general supplements such as “Iron Tek: Growth Tek.”

Chemical Composition

Melatonin, scientifically named N-acetyl-5-methoxytryptamine, is synthesized from the amino acid tryptophan. From tryptophan, it is converted into 5-hydroxytryptophan, then serotonin, and finally to Melatonin (3).

Mechanisms of Action

Although for many years it was assumed that the main purpose of Melatonin was to regulate sleep patterns and the body’s circadian rhythm, it is clear now that melatonin has a wide spectrum of biological activities. Melatonin is light sensitive and its production is influenced by day/night cycles: light inhibits melatonin secretion and darkness stimulates secretion. Peak release of melatonin occurs during the night with the lowest levels occurring midday (4). Melatonin appears to increase the binding of gamma-aminobenzoic acid (GABA) to its receptors in the brain which is one way it may exert various effects. Additionally, melatonin may decrease neurotransmission by a direct effect on selected nerve cells (5). Endogenous melatonin is involved in several other functions including growth hormone secretion (6) and direct antioxidant activity (7). Unlike most antioxidants, melatonin has no pro-oxidative activity and all known intermediates generated by the interaction of melatonin with reactive species are also free radical scavengers (7). Thus, many different mechanisms are responsible for the multiple actions of melatonin.

Reported Uses

Oral melatonin is used for many reasons, including jetlag, insomnia, shift-work and circadian rhythm disorders, circadian rhythm sleep disorders in blind children and adults, and for benzodiazepine and nicotine withdrawal (1-4). It is also used to induce sleep in persons with depression, schizophrenia, Alzheimer's disease, and other disorders. Similarly, it is used by persons with depression, chronic fatigue syndrome (CSF), migraine and cluster headaches, osteoporosis, and cancer (3). Melatonin serves as an antioxidant, with a potency several times greater than vitamin C and E in protecting tissues from oxidative injury when compared at an equivalent dosage (5). This endogenous hormone is also taken to retard the aging process and increase sex hormone secretion (1-7). Lastly, melatonin can be used topically as a skin protectant against UV light, and intramuscularly used for treating cancer (1)

Dosage

The dosage of Melatonin depends upon the specific use, but the range is 0.5 to 50 mg. Reported doses for insomnia are 0.5 – 3 mg at bedtime; for jetlag: 0.5 – 5 mg at bedtime on arrival day and usually two to five days following. A 5 mg dose has been shown to affect pituitary function (7). Higher doses (up to 50 mg) have been used for clinical conditions such as tardive

dyskinesia, solid tumors, cluster headaches, and during chemotherapy. High doses (50 mg or more) should never be taken without physician approval.

Scientific Evidence

Numerous human and animal studies have been conducted over a broad range of topics related to melatonin. The most well studied uses are in the area of sleep, insomnia, and jetlag (8,9). With respect to jetlag, the amount and timing of supplementation are important. Petrie et al. (8) showed that air crew taking 5 mg of melatonin for five days at the start of an international flight reported significantly less jetlag and sleep disturbance following the flight compared to placebo and a group that started taking melatonin three days prior to the flight. The group that started the melatonin early reported a worse overall recovery than placebo. However, not all jetlag studies are consistent, so no definitive recommendations can be made. This is also true of induction of sleep. Hughes et al. (10) reported that although melatonin had a positive effect on sleep latency, it was not effective in sustaining sleep or improving subjective self-reports of nighttime sleep and daytime alertness. Clearly more work is needed in these areas.

In a recent review, Atkinson et al. (11) discussed how age and fitness status may confound research related to melatonin and exercise. Clearly the administration of exogenous melatonin should compromise short-term mental and physical performance because of the hypnotic and hypothermic effects. In contrast, it has been hypothesized that the hypothermic effects of melatonin may improve endurance performance in hot environments. Although this is not supported by studies involving military recruits, the exercise was at a low intensity. Further work will be needed in this area.

Other literature has evaluated associations between melatonin and antioxidant actions, but no data directly support supplementation. The use of melatonin in preventing hyperoxia-induced pulmonary damage has been proposed and tested in rats, but the results cannot be generalized to humans. A body of literature has focused on the anticarcinogenic effects and use of melatonin as a cancer treatment (12-14), primarily because of its antioxidant properties. Preliminary studies have shown that melatonin inhibited breast cancer cells in test tubes and put some breast cancer patients into remission (13,14). Significant levels of melatonin have also been shown to reduce the amount of prostate specific antigen (PSA) in men (12). Finally, genetic research involving several different aspects of melatonin receptors and signalling is becoming more prevalent in the literature (15). It will take many years of research, both animal and human to define all of the roles that supplemental melatonin might serve.

Adverse Reactions

CNS: Headache, transient depressive symptoms, daytime fatigue, drowsiness, dizziness, irritability, reduced alertness, confusion

CV: Hypotension

GI: Abdominal cramps, nausea, vomiting

GU: May reduce male sex drive and interfere with HRT

Due to the possibility of contamination, animal sources of melatonin should not be taken.

Drug Interactions

All information regarding interactions is derived from reference 3.

- Benzodiazepines: Avoid taking the two together as benzodiazepine administration might decrease melatonin levels.

- **Beta Blockers:** Melatonin can reverse the negative effects of such beta-blockers as propranolol and atenolol on nocturnal sleep.
- **Caffeine:** Caffeine decreases melatonin levels so taking both concurrently would theoretically decrease the effectiveness of melatonin.
- **Herbs/Supplements:** Some of these that have sedative affects might enhance the therapeutic and adverse properties of melatonin.
- **Immunosuppressants:** Since melatonin stimulates the immune system, it might cancel the effects of immunosuppressive drugs.
- **CNS Depressants:** Combining Melatonin with alcohol or other sedative drugs can have an additive sedative effect.
- **Fluoxetine (Prozac):** Use of melatonin with Fluoxetine has been shown to improve the sleep of some people with major depressive disorder.
- **Fluvoxamine (Luvox):** Fluvoxamine will not only increase Melatonin levels in the body, but will also increase the bioavailability of exogenously administered Melatonin. The effects of this are contradictory among researchers; some believe this may produce a beneficial interaction potentially useful for refractory insomnia, while others believe this interaction may cause excessive drowsiness and adverse effects.

Contraindications

People with autoimmune diseases, allergies, cardiovascular disease, depression, epilepsy or other seizure disorders, liver disease and a history of drug or alcohol abuse should all avoid taking melatonin. Melatonin can also worsen hypertension in those already taking antihypertensive medications (1).

Young children should not be given melatonin supplements. Women trying to conceive should avoid high doses of melatonin because they have been associated with altered ovarian function and anovulation. Women who are pregnant or breastfeeding should also avoid melatonin supplements. Finally, driving and operating other machinery should be avoided while taking melatonin.

Comments

Safety concerns about melatonin have lead to restricted sales in the UK and banning in Japan. Since melatonin is not considered a drug, it is not approved/controlled/regulated by the FDA. Melatonin has FDA orphan drug status for circadian rhythm sleep disorders in blind children and adults.

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2. Creatine

Sources

Creatine is found in dietary sources such as red meat, milk, and fish, and is manufactured endogenously in the kidneys, liver, and pancreas (1). Some supplement formulas containing creatine are Crea Drive, Crea Stack, Creatine Burst, Meta Cel, Cell Fit, Creatine Sport Gel, Femme Advantage Creatine Serum, Creatine Blast, Creagen, Xtra Advantage Creatine Serum and others. Most supplement products are simply labeled as Creatine Monohydrate.

Chemical Composition

Creatine is an amino acid synthesized from arginine and glycine. Skeletal muscle contains the highest levels of creatine, in the form of creatine phosphate. High levels of creatine are also found in the heart, brain, kidneys, and smooth muscle.

Mechanisms of Action

Creatine, an energy substrate, is used to maintain high levels of intracellular ATP for muscular contraction during high intensity exercise (1-4). Depletion of ATP leads to muscular fatigue, and regenerating ATP at the same rate as utilization may delay muscular fatigue. Oral ingestion of creatine monohydrate has been shown to increase the plasma creatine pool so that it can be used to resupply muscular energy levels.

Reported Uses

Creatine is promoted for improved athletic performance, increasing muscle mass, improving congestive heart failure, neuromuscular disease, mitochondrial cytopathies, hyperlipidemia, ALS, McArdles disease, and various muscular dystrophies.

Dosage

Creatine is typically taken at 20 g/day (0.3 g/kg) for 5 days followed by a maintenance dose of 2 g/day for enhancement of athletic performance. Water intake during creatine supplementation should be at least 64 ounces per day.

Scientific Evidence

Creatine has been studied since the early 1920's, but an interest in creatine supplementation developed in the 1990s due to the potential for enhancement of certain types of exercise performance. Many studies have examined the effects of creatine on athletic performance (5-14), and many have found a positive effect (5-10). In a meta-analysis, 100 studies were reviewed for body composition and performance changes by using a selection criteria of randomization, placebo control, and blinded to subjects (5). Creatine supplementation was found to increase lean body mass and upper-body exercise strength, however, it was not effective in improving running and swimming performance. Creatine supplementation has also been shown to improve isometric strength and body composition in older adults (6). Twenty-eight adults (>65 years) participated in a whole-body exercise program 3 days/week for 14 weeks and either received creatine (5 g/day +2 g dextrose) or placebo (dextrose only). At the end of the trial the creatine supplemented group had greater increases in fat-free mass and gains in several indices of isometric muscle strength. When elite rowers and wrestlers were the participants, significant increases in endurance and anaerobic performance in those supplemented with creatine compared to placebo were noted (7,11). Most studies examining creatine supplementation have shown encouraging results with respect to improvements in high intensity, anaerobic types of activities, but continued research is needed with larger numbers of subjects.

Some efforts have focused on both short-term creatine loading and long-term use relative to its effect on exercise capacity (12,13). One study examined body composition, fuel selection, sprint and endurance performance during creatine supplementation (12). Twenty subjects were given creatine or a placebo for a 5 day loading period (20 g/d) followed by 6 weeks at 2 g/d. Both short- and long-term creatine supplementation resulted in improved performance of repeated supramaximal sprints on a cycle ergometer and increases in fat-free mass. The results did not show an increase in muscle or whole-body oxidative capacity or performance during endurance cycling. In another study, the short-term effects of creatine loading and long-term effects of supplementation on the performance of military tasks, thermoregulation, and health risks by soldiers was evaluated (13). Sixteen subjects were assigned to a creatine (20 g/day) or placebo group for 6 days and then 6 g/day for four weeks. Body composition and core temperature were measured during a 10-mile march, 5-mile run, and performance of physical tasks. The investigators found that body mass and number of pull-ups increased significantly in the creatine group but no significant differences were found for any other factor. It was concluded that creatine would not enhance the overall readiness or performance of soldiers during military operations.

Only one study has investigated creatine supplementation in women (9). Kambis et al. (9) examined quadriceps muscle function, thigh circumference, and body weight in 22 college age women after supplementing with 0.5 g/kg fat-free mass or placebo for five days. Results from the study demonstrated that supplementing with creatine increased mean power for knee extension and flexion but did not alter body fat, quadriceps circumference, and/or total body weight. The results of this study suggest that men and women may respond similarly to creatine supplementation.

One big question relates to the safety of long-term creatine supplementation, and such questions have been asked by multiple researchers (12-14). The information to date indicates that in normal, healthy individuals the kidneys are able to excrete creatine and its end products with no adverse affects. One study did indicate a concern that creatine is metabolized into

formaldehyde and that chronic administration of a large amount of creatine could cause serious side-effects (14). This possibility has not been demonstrated.

Adverse Events

CNS: Seizure

CV: Cardiomyopathy, arrhythmias, cardiac arrest.

GI: Gastrointestinal pain, nausea, diarrhea, kidney problems

Musculoskeletal: Cramping, rhabdomyolysis.

The FDA has received over 32 complaints linked to creatine, but causality has not been proven (1).

Drug Interactions

Some reports have indicated that high doses of creatine may adversely affect kidney function. If creatine is combined with drugs that may be nephrotoxic, there could be an additive harmful effect (1).

Contraindications

Persons with pre-existing renal disease should not take creatine nor should anyone who has a disease that comprises kidney function such as diabetes. Not recommended for children or for women who are pregnant or lactating.

Comments

Creatine is currently not banned by the International Olympic Committee, NCAA or any other sports organization. These organizations have stated that insufficient medical evidence exists to support a clear harm to users. California is considering a ban on the sale of creatine to anyone under the age of 18 and that manufacturers place an adverse effects warning label on all creatine-containing products. Recent scientific research has provided more information on creatine's efficacy, however, new adverse events have also been reported. Anyone considering using creatine must weigh the pros and cons before making a decision.

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3. Glucosamine/Chondroitin Sulfate

Sources

Chondroitin Sulfate is manufactured from some natural sources, such as shark and bovine cartilage (1-4). Commercially available sources of glucosamine are derived from chitin, the specially processed exoskeleton of shrimp, lobster, and crab. Glucosamine supplements include Syn-flex, Joint Juice, and Osteo-Bi-Flex. Common chondroitin sulfate products, include NOW Chondroitin Sulfate and Chondroitin Sulfate 400, and Cosamin. Supplements such as ArthxDS Glucosamine Chondroitin and Maximum Strength Flex-A-Min contain both substances.

Chemical Composition

Chondroitin Sulfate is made up of glucuronic acid and galactosamine, under the class of molecules called glycosaminoglycans (1-4). Glucosamine is an aminopolysaccharide, which means it is a combination of an amino acid (glutamine) and a sugar (glucose).

Mechanisms of Action

Chondroitin sulfate and glucosamine are related in structure and function. Chondroitin sulfate is naturally found in the cartilage and tissue of most mammals and serves as a substrate in the formation of a joint matrix structure. Chondroitin is thought to relieve joint pain, improve joint stiffness and walking speed, and possibly slow the progression of cartilage degradation in knee joints by stopping certain enzymatic actions and increasing the production of proteoglycans (1-4).

Glucosamine, which may stimulate the metabolism of chondrocytes in articular cartilage and in synovial tissues, is required for building glycoproteins, glycolipids and glycosaminoglycans, the materials found in tendons.

Reported Uses

The main uses of glucosamine are to relieve, treat, or prevent osteoarthritis, temporomandibular joint arthritis, and weight loss. Chondroitin is used for treating osteoarthritis, as well as ischemic heart disease, osteoporosis, and hyperlipidemia. A variety of oral (pill and liquid) supplements, as well topical creams, containing these substances are on the market.

Dosages

Since Glucosamine/Chondroitin Sulfate is not regulated by the FDA, each manufacturer supplies its own directions and indications. Recommended dosages are dependent upon the intended uses. The typical dose of a chondroitin supplement for osteoarthritis is 200-400 mg two or three times a day, or a single 1000-1200 mg dose, whereas a normal dose of glucosamine for osteoarthritis is about 1500 mg a day split up into three doses.

Scientific Evidence

Most of the literature and recent research has focused on using these agents to treat osteoarthritis (1-12). The majority of studies indicate that taking glucosamine sulfate orally, for a few weeks to three years, can significantly improve symptoms of pain and functionality indices in patients with osteoarthritis of the knee and other joints (5,6). In addition, glucosamine sulfate appears to be at least as effective as analgesic doses of ibuprofen for relieving pain and improving temporomandibular joint function, such as chewing, yawning, talking, and laughing (7,8). One study also suggests that a combination of glucosamine and chondroitin sulfate may be useful in regeneration of spinal disks (9), but this has not been documented.

In contrast, although studies consistently show that glucosamine relieves arthritis joint pain, the latest evidence indicates that glucosamine does NOT cause regeneration of cartilage in osteoarthritis (10). Moreover, glucosamine does not appear to be effective when used orally for reducing pain in severe, long-standing osteoarthritis (6). This is derived from one study wherein glucosamine sulfate was added to an existing analgesic regimen, and its addition failed to improve symptoms of osteoarthritis compared to placebo after two months of treatment. However, the patients were generally older, heavier, and had more severe and a longer-duration of osteoarthritis than patients in previous studies with positive findings (6).

In summary, both of these agents, alone and in combination need further work. The possibility for success is great, but because less research is being done on chondroitin, more information is needed about its structural effects as well as its possibility in terms of structural regeneration (11,12).

Adverse Reactions

Chondroitin Sulfate is usually well tolerated when taken orally.

CNS: Headaches, drowsiness

CV: Extrasystoles, edema

GI: Nausea, vomiting, constipation, diarrhea

Skin: Skin reactions

Other: May increase cholesterol/ triglyceride levels, and blood pressure

Drug Interactions

All drug interactions are derived from reference 3.

- Anti-Diabetic Drugs: Glucosamine sulfate might decrease insulin production so dosage adjustments might be necessary.
- Antiplatelet/Anticoagulant Drugs: Concurrent use of chondroitin sulfate might increase the risk of bleeding.
- Cancer Chemotherapy Drugs: Glucosamine may induce resistance to certain chemotherapy drugs.
- Hyaluronic Acid: Taken with chondroitin sulfate causes a beneficial synergistic effect in cataract surgery.

Contraindications

Women who are pregnant or lactating should avoid glucosamine/chondroitin products, as there is insufficient information. Persons allergic to shellfish should consult their doctor before taking glucosamine. Children should also not take either glucosamine or chondroitin. People with bleeding disorders should avoid taking chondroitin sulfate because of an increased risk of bleeding (3).

Comments

Although glucosamine and chondroitin sulfates are marketed together, there is no evidence that the combination of the two has any greater effect than either substance alone (3). Glucosamine sulfate per se has been more carefully studied for osteoarthritis than any other forms of glucosamine and/or chondroitin sulfate. Avoid N-Acetyl Glucosamine because there is no evidence that this compound helps with osteoarthritis. That glucosamine and chondroitin are safe, and in many cases effective, are grounds for further study to determine optimal dosing, interactions, and mechanisms of action. However, clinicians should be aware that the purity of the ingredients, reputation of the manufacturer, and the molecular weight of chondroitin supplied are very important (13).

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4. Gugulipid

Sources

Gugulipid is derived from the gummy resin of an ancient herb, the mukul myrrh tree (*Commiphora mukul*); it is most abundant in India. In India, gugulipid is available by prescription under the trade name Guglip. Gugulipid formulas available over-the-counter in the United States include Ultra Guggulow, Guggal Cholesterol Compound, Guggul Gum Resin, Guggulsterones, Choles-Response, Gugulplus, HeartCare, GlucoCare, and LeanCare.

Chemical Composition

The resin is harvested and then oleoresin is extracted. The extract (gum guggul) contains several active components, most notable, the guggulsterones, which are thought to act as cholesterol and triglyceride-lowering agents. Other names are Guggal, Guggul Gum Resin, Guggulipid, Guggulipids, Guggulu, Guggulsterone, Guggulsterones, Gum Guggal, Gum Gugglu, Gum Guggulu, Indian Bdellium-Tree, Mukul Myrrh, Mukul Myrrh Tree (1).

Mechanisms of Action

The guggulsterones, found in gugulipid, are potent antagonists of the farnesoid X receptor (FXR), a nuclear hormone receptor activated by bile acids and involved in cholesterol metabolism (2). The result of this blocking action is to increase the liver's metabolism of low-density lipoprotein (LDL) cholesterol, thus reducing its accumulation in the circulation.

Reported Uses

Gugulipid was traditionally used in India in the Ayurvedic tradition to treat obesity and arthritis. Most recently, gugulipid has been touted for its efficacy in lowering LDL cholesterol, raising high-density lipoprotein (HDL) cholesterol, and decreasing serum triglycerides. This compound is also thought to have weight loss, antioxidant, and anti-inflammatory properties that may help fight obesity, aging, and alleviate arthritis.

Dosage

The typical dose is 50 mg of guggulsterone twice daily.

Scientific Evidence

Very few controlled trials using gugulipid have been conducted to date. The literature from India indicates that gugulipid (guggul) has anti-hypercholesterolemic effects (3,4,5). One study examined administration of 50 mg Gugulipid or placebo in 61 patients with hypercholesterolemia on a controlled vegetarian diet (5). Gugulipid decreased total cholesterol by 11.7%, LDL by 12.5%, triglycerides 12%, whereas the levels were unchanged in the control group. Lipid peroxides declined by 33% in the gugulipid group, without any decrease in controls. The researchers reported that at 36 weeks, the combined effect of diet and gugulipid was as effective at lowering cholesterol levels as drug therapy. However, a recent study in the United States did not find any benefits in persons with hypercholesterolemia (6). Supplementation with guggulipid did not improve serum cholesterol levels over the short term and may have actually increased levels of LDL-C (6). The authors also noted that guggulipid appeared to cause a dermatologic hypersensitivity reaction in some patients.

Other cardioprotective benefits of gugulipid have been reported (2,7,8). An animal study was conducted based on the hypothesis that guggulsterone antagonizes the FXR, a nuclear hormone receptor activated by bile acids. The results showed that treatment with guggulsterone decreased hepatic cholesterol in wild-type mice fed a high-cholesterol diet, but did not affect FXR null mice (2). The researchers concluded that blocking FXR activation was the basis for the cholesterol-lowering activity of guggulsterone. In a review by Miller (8), there was a discussion about a human study wherein combination of *Inula racemosa*, another traditional Ayurvedic botanical with potential cardioprotective benefit, and gugulipid was used. It was reported that the combination was superior to nitroglycerin in reducing the chest pain and dyspnea associated with angina (8). Finally, other studies have considered gugulipid as an aid in controlling arthritis-related inflammation (9). Overall, the data are very interesting and suggest that more studies should be conducted.

Adverse Events

CNS: Restlessness, anxiety and headaches

GI: Nausea, gas, hiccups, and diarrhea

Drug Interactions

No reported drug or nutrient interactions with gugulipid have been reported.

Contraindications

Not recommended for patients with liver disease, or inflammatory bowel disease. Also not recommended for children or for women who are pregnant or lactating.

Comments

Limited research has been conducted on this relatively new product. Preliminary research is favorable but far from conclusive. Further controlled studies are needed before recommendations can be made.

Consumers should be careful to purchase products labeled as gugulipid supplement and not guggul or guggulu, as these compounds are unrefined forms of the resin and could be toxic. Also, different spellings are routinely used - guggulipid and gugulipid.

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5. S-Adenosyl-L-Methionine (SAmE)**Sources**

SAmE (multiple suppliers), SAmE Jointplex. There are no significant dietary sources of SAmE (1-4).

Chemical Composition

S-Adenosyl-L-methionine (SAmE) can be synthesized when the amino acid L-Methionine, folic acid, vitamin B₁₂, and trimethylglycine are all available, and there is adequate adenosine triphosphate (ATP) to activate methionine. Methionine is an essential amino acid that can be derived endogenously or from the metabolism of dietary protein. SAmE is also known as ademetionine, adenosylmethionine, S-adenosyl methionine, S-adenosylmethionine, SAM-e, and Sammy (1-4).

Mechanisms of Action

SAMe, an integral component of the metabolic machinery of all living cells, contributes to the synthesis, activation, and/or metabolism of hormones, neurotransmitters, nucleic acids, proteins, phospholipids, and some drugs (1-4). It functions in three main pathways: methylation, transulfuration, and aminopropylation (4). SAMe serves as the sole methyl donor in numerous methylation reactions, including the synthesis of creatine from guanidinoacetate, phosphatidylcholine from phosphatidylethanolamine, and epinephrine from norepinephrine. The end product of all SAMe-dependent methylation reactions is homocysteine, which can be converted to cystathionine. Cystathionine can be converted into glutathione, by the first step of the transulfuration pathway, or it can be recycled back to methionine. Glutathione serves as the main cellular antioxidant molecule within the body.

SAMe also plays an important role in the synthesis of polyamines via the aminopropylation pathway. SAMe is metabolized and converted to the polyamines spermidine and spermine, which are involved in the control of cell growth and may have analgesic and anti-inflammatory properties (1-4). During aminopropylation, one of the metabolites is converted back to methionine, a salvage route to conserve methionine (4,5).

SAMe synthesis is closely linked to vitamin B12 and folate metabolism, and lack of these nutrients may compromise SAMe levels. Other conditions, such as liver disease and AIDS-related myelopathy are two conditions wherein supplementation with SAMe can raise endogenous levels back to the normal range and alleviate symptoms (1).

Reported Uses

Oral: SAMe has been used primarily to treat depression and osteoarthritis. Other uses include heart disease, fibromyalgia, bursitis, tendonitis, chronic low back pain, dementia, Alzheimer's disease, slowing the aging process, antioxidant maintenance, improving intellectual performance, Parkinson's disease, attention deficit-hyperactivity disorder, multiple sclerosis, spinal cord injury, seizures, migraine headache, chronic lead poisoning, disorders of porphyrin, and bilirubin metabolism (1-4).

Intravenous: SAMe has been used to treat depression, osteoarthritis, AIDS-related myelopathy, fibromyalgia, liver disease, cirrhosis, and intrahepatic cholestasis (1-4).

Intramuscular: SAMe has been used to treat fibromyalgia, depression, and Alzheimer's disease (1).

Dosage

Oral: Most recent studies use 200-400 mg three times/day to 1600 mg/day (6,7).

Parenteral: 400 to 800 mg per day intravenously (IV) or intramuscularly (IM) (1,7) have been used.

Scientific Evidence

SAMe is an interesting compound that has been used in Europe for many years. It has many reported benefits (5,6,7,8), but not all uses have been carefully studied. Delle et al. (8) conducted two multicenter studies to test the efficacy of oral and intramuscular SAMe versus imipramine (150 mg per day) for treating major depression. The first study used SAMe orally at a dose of 1,600 mg per day and the second study used SAMe 400 mg IM per day. The outcome measures for the two agents were similar, with the additional benefit that there were significantly fewer adverse effects in patients who were treated with SAMe versus imipramine. Also, both doses of SAMe were comparable.

Soeken et al. (7) conducted a meta-analysis on 12 randomized controlled trials that tested the efficacy of SAME as compared to placebo and NSAIDs in osteoarthritis. The outcomes, pain and functional limitation were comparable in the SAME and NSAIDs groups, but SAME was without the adverse effects often associated with NSAID therapies (7).

Two studies have examined SAME in the treatment of patients with primary fibromyalgia (8,9). Jacobsen et al. (8) used 800 mg of SAME per day orally versus placebo for six weeks and Volkmann et al. (9) used 600 mg of SAME per day intravenously for 10 days. Jacobsen et al. (8) found improvement in the clinical disease activity, pain experienced during the last week, fatigue scores, morning stiffness and mood in the actively treated group as compared to placebo. In contrast, Volkmann et al. (9) found no significant difference in any primary outcome measures between the two treatment groups.

Other areas of interest related to the use of SAME in HIV and liver disease (11-16). Castagna et al. (11) administered 800 mg of SAME per day intravenously to HIV-infected persons for 14 days and reported significant increases in cerebrospinal SAME and GSH. They postulated that the use of SAME may be protective against SAME and GSH deficiency in the CNS of HIV-infected patients. In other studies, the effect of SAME on liver disease has been evaluated (12,13). Mato et al. (12) conducted a multicenter, randomized, placebo-controlled, double blinded, clinical trial testing SAME supplementation in patients with alcoholic cirrhotic livers. They studied 123 patients who received SAME orally at a dose of 1,200 mg per day or placebo for 2 years and concluded that long-term treatment with SAME may improve survival or delay liver transplantation in patients with alcoholic cirrhotic livers, especially in those with less advanced liver disease (12). This is also supported by other reviews (13,14).

In another study, Almasio et al. (15) reviewed the role of SAME as a therapy in the treatment of cholestasis associated with liver disease: a total of 639 patients with cholestasis due to acute or chronic liver disease were studied in four clinical trials. They reported that SAME, as an intravenous dose of 800 mg/day or an oral regimen of 1.6 g/day for 2 weeks, was superior to placebo in relieving the symptom of pruritus and in restoring serum total bilirubin and serum alkaline phosphatase towards normal. What is very clear is that SAME has multiple roles and research is needed to document the effects of this agent on a variety of other medical issues.

Adverse Reactions

CNS: Headache, mild insomnia, dizziness, nervousness, anxiety, depression and hypomania in people with bipolar disorder (1).

GI: Flatulence, nausea, vomiting, diarrhea, constipation, anorexia

Other: Dry mouth, sweating

Drug Interactions

- Analgesics with Serotonergic Activity: Could increase effects of drugs and other supplements that increase serotonin levels: 5-hydroxytryptophan, Hawaiian baby woodrose, L-tryptophan, St. John's wort, meprobamate, pentazocine, tramadol, imipramine, fluoxetine, paroxetine, sertraline, other antidepressants, dextromethorphan, and monoamine oxidase inhibitors.
- Concurrent use of SAME and any of the above drugs could cause cerebral vasoconstriction disorders (1).
- Levodopa (Dopar, Larodopa): Might reduce effectiveness in the treatment of Parkinson's disease, but has not been shown in humans (1).

- MAOIs: Concomitant use might have additive adverse effects similar to that of conventional antidepressants.

Contraindications

SAMe should not be taken by people on MAOIs and for two weeks after discontinuing MAOIs (1).

Comments

This is a most fascinating compound with potentially many benefits.

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6. 5-Hydroxytryptophan (5-HTP)

Sources

5-HTP is not found in any significant level in a normal diet, but the body converts tryptophan into 5-HTP. Most manufacturers label their products as simply 5-HTP, 5HTP, 5 HTP, 5-hydroxytryptophan, L-5 HTP, or Oxitriptan.

Chemical Composition

5-HTP used in dietary supplements is derived from the seeds of an African plant, Griffonia Simplicifolia. In the body, tryptophan is converted to 5-HTP by adding a hydroxyl group to the 5-position.

Mechanisms of Action

5-HTP is a precursor for serotonin, a potent neurotransmitter in the brain. It is theorized that supplements of 5-HTP can increase serotonin levels and influence mood, sleep patterns, and pain control.

Reported Uses

5-HTP has been promoted for relief of mild to moderate depression, insomnia and sensation of pain due to migraines, fibromyalgia and general muscle pain. It is also purported to promote restful sleep and weight loss by suppressing appetite.

Dosage

Typical dose is 150-900 mg per day, usually in 2-3 doses. A dose of 100 mg three times per day has been used with no adverse events.

Scientific Evidence

The overall scientific evidence for the effectiveness of 5-HTP is weak at best. Some studies have shown that 5-HTP is as effective as prescription antidepressant medications for alleviating mood disturbances (1,2,3). Other studies report no change in mood when supplemented with 5-HTP (4,5). The benefits derived from 5-HTP in reducing pain were investigated in the dosing range of 300-900 mg/day, where it was shown to be effective in alleviating migraines, reducing appetite and promoting sleep (3,6,7). One animal study combined 5-HTP with fluoxetine, an SSRI medication, to investigate the combined effects on appetite and weight loss (7). It was hypothesized that 5-HTP would increase serotonin synthesis and that the SSRI action would keep levels of serotonin elevated and result in greater weight loss than with fluoxetine alone. The study did find a significant reduction in food consumption with the combined treatments.

Adverse Events

CNS: Headaches, lethargy

GI: Nausea, GI distress

Musculoskeletal: Muscle pain

Other: Remote possibility for contamination with a compound linked to a disorder known as eosinophilic myalgia syndrome (EMS).

Drug Interactions

- Individuals taking prescription anti-depressants, weight control medications or herbal remedies for depression should not combine these treatments with 5-HTP supplements without the advice of a physician.

Contraindications

Not recommended for children or for women who are pregnant or lactating.

Comments

In 1998 FDA scientists confirmed and published a point paper noting the presence of impurities in some 5-HTP products that were being promoted as dietary supplements. One of the impurities, known as “peak X”, had previously been identified in one case of the illness eosinophilia-myalgia syndrome (EMS) associated with 5-HTP in 1991. Impurities similar to

“peak X” were also found in L-tryptophan-induced illnesses associated with a 1989 epidemic of EMS. In the fall of 1989 L-tryptophan was recalled by the FDA and in 1990 the FDA banned the sale of L-tryptophan because of EMS. The exact cause of the 1989 epidemic and the EMS case associated with 5HTP remains unclear, but the ban continues today. Many are certain that EMS was caused by the impurity, perhaps “peak X”.

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7. Choline

Sources

Major food sources contain choline, including egg yolks, organ meats, legumes (2), liver, muscle meats, fish, nuts, and peas (1). Countless dietary supplements also contain choline as a minor ingredient or main component.

Chemical Composition

Choline is a quaternary amine traditionally considered in the B-vitamin class. It is produced in the liver via the methylation of phosphatidylethanolamine (1-3). Choline is also known as Choline Bitartrate, Choline Chloride, Intrachol, Lipotropic Factor, Trimethyl-ethanolamine, and trimethylammonium hydroxid.

Mechanisms of Action

Choline serves as the precursor for several important substances within the body: phosphatidylcholine and sphingomyelin (two important components of biological membranes); diacylglycerol and ceramide (important intracellular messengers); platelet-activating factor and sphingosylphosphorylcholine (signaling lipids); and acetylcholine (a neurotransmitter). Betaine, a choline metabolite, serves as the methyl donor in the resynthesis of methionine from homocysteine (1,2,3). Choline is found throughout the body in most tissues but there is high concentrations found within nervous tissue. Choline is thought to play a major role in the birth, death, and migration of cells into the hippocampus during fetal development and probably has a major impact on the distribution and morphology of neurons responsible for memory (4,5). Choline is also thought to have an anti-inflammatory effect by lowering lipophosphatidylcholine levels. This is the mechanism by which choline is thought to reduce symptoms in asthma. Choline may play a role in cancer prevention, and feeding a choline-free diet to animals has been implicated in the development of hepatocellular carcinoma (5).

Reported Uses

Choline is marketed as an oral supplement to enhance athletic performance by increasing energy and delaying fatigue in endurance sports and for use in bodybuilding. It has also been marketed medically in the treatment of liver disease including chronic hepatitis and

cirrhosis, brain development and function including depression, memory loss, Alzheimer's disease, dementia, schizophrenia, Huntington's chorea, Tourette's syndrome, cerebellar ataxia, and complex partial seizures. Other uses include treatment of hypercholesterolemia, asthma, cancer prevention, cardiovascular protection, and as a supplement in infant formulas (1-4). The FDA has given orphan drug status to intravenous choline chloride for TPN-associated hepatic steatosis (6).

Dosage

Daily adequate intake requirements of choline were established by the Food and Nutrition Board, Institute of Medicine of the National Academy of Sciences in April 1998 and varies as a function of age (See references 7 and 8).

Doses ranging from 500-1000 mg three times per day have been used but an optimal dosage has not been established (7). In addition, the dose should not to exceed 3.5 grams per day for adults over age 18 (7).

Scientific Evidence

It was hypothesized that choline supplementation would delay fatigue, but none of the studies conducted have demonstrated any benefit. Spector et al. evaluated the performance of 20 male cyclists who underwent supramaximal brief and submaximal prolonged activities with and without choline bitartrate supplementation. Fatigue times and work performed under the test conditions were similar, so they concluded that cyclists either do not deplete choline during supramaximal brief or prolonged submaximal exercise or no benefit is derived from choline supplementation (9). Similarly, Deuster et al. (10) studied the effects of choline ingestion on cognitive performance, aerobic endurance, muscle strength and endurance, and anaerobic capacity. No differences between placebo and choline conditions were noted for any of the performance parameters, either physical or cognitive.

Multiple studies have been conducted testing the effects of choline on brain development and memory. Zeisel et al.(5,11,12) have tested the effects of choline supplementation in an animal model in utero or during the second week of life compared to those without supplementation. They noted that rat pups supplemented with choline had a change in brain function which resulted in lifelong memory enhancement (11,12), and concluded that choline stores can become depleted in pregnant and lactating animals, and failure to provide adequate choline can compromise brain development (11,12).

In addition to brain development, studies have looked at the effect of choline on cancer prevention (13) and asthma (14,15). Albright et al. (13) tested the effects of a choline deficient environment on rat hepatocytes and found that cells with no choline underwent apoptosis, whereas cells adapted to survive in low choline environment were resistant to apoptosis and able to grow uncontrollably. They concluded that normal choline levels are required for apoptosis and that diets deficient in choline were likely to undergo malignant transformation (13).

Gupta et al. (14) and Gaur and Gupta (15) studied the use of choline for the management of asthma. One study tested choline in two different dosages versus a placebo (14) and the other study tested choline versus di-sodium cromoglycate (15). Both studies looked at improvement in subjective symptoms and objective data (specific airway conductance) and concluded that choline was useful as a prophylactic drug in the management of bronchial asthma. Neither study established an optimal dose of choline for treatment of asthma. This may be important to the diving community in that bronchial hyper-responsiveness (BHR) is fairly

common and constitutes a contraindication to diving because it may promote pulmonary barotrauma (16).

Lastly, administration of choline may be essential for preventing parenteral nutrition-associated hepatic dysfunction (17,18). Buchman et al. (17) administered 2 g of choline chloride for 24 weeks to seven patients who had been on total parenteral nutrition (TPN) for an extended time. Their results indicated that choline may be required for long-term TPN patients, and that a choline deficiency may contribute to the development of TPN-associated liver disease. Specifically they concluded that hepatic steatosis associated with parenteral nutrition could be ameliorated, and possibly prevented, with choline supplementation (17).

Adverse Reactions

CV: Hypotension

GI: Gastrointestinal distress, vomiting, diarrhea

Other: Fishy body odor, sweating, salivation, hepatotoxicity.

Drug Interactions

None are known at this time.

Contraindications

Individuals with trimethylaminuria, renal disease, liver disease, depression and Parkinson's disease may experience adverse effects when intakes approach the upper limit (7,8).

Comments

Although adequate dietary intake guidelines have been set for choline, there are few data to assess whether a dietary supply of choline is needed during all stages of life (7,8).

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8. Dibencozide or Cobamamide

Sources

Dibencozide is derived naturally from yeast, liver, microorganism fermentation products, and animal proteins, such as organ and muscle meats, dairy products and eggs, and sea foods. It is heavily marketed by health food stores under names such as B₁₂ NeuroBolic, Dibencozide, Ironplex, Cognimax (1).

Chemical Composition

Dibencozide, a biologically active cobalamin, is part of the Vitamin B₁₂ or cobalamin coenzyme family. Vitamin B₁₂ encompasses some of the most structurally complex small molecules made in nature, and contains a central cobalt atom, which is why the family of molecules are collectively known as cobalamins. Various forms of cobalamin exist, including methyl-, cyano, adnosyl- and hydroxocobalamin (B_{12b}), and sulphito and aquacobalamins (B_{12c}). Only two cobalamins are active as coenzymes in the human body: adenosylcobalamin and methylcobalamin, and the body can usually convert from one form to the other. Although most of the B₁₂ present in animal tissues is in one of those two coenzyme forms, the most common forms found in food sources are cyanocobalamin and hydroxocobalamin (1,2).

Mechanisms of Action

Cyanocobalamin is the most stable of the cobalamins and is metabolized to an active coenzyme (1,2). Vitamin B₁₂ is involved in fat, protein, and CHO metabolism and is active in all cells, particularly in the bone marrow, CNS, and GI tract.

Reported Uses

Dibencozide is marketed as a supplement to enhance protein metabolism and thereby increase muscle mass and strength. It has also been marketed as an aid in mental function by increasing concentration, treating depression, anxiety and panic attacks (1).

Dosage

The doses vary dramatically according to manufacturer. No cases of toxicity from excessive cobalamin ingestion have been reported (1-6).

Scientific Evidence

No studies to date have specifically tested dibencozide for efficacy in any regard.

Adverse Reactions

No adverse reactions have been reported.

Drug Interactions

- Acid inhibiting drugs: can decrease absorption from the gastrointestinal tract (cimetidine, omeprazole, etc....)
- Many agents will decrease absorption including aminoglycosides, aminosalicic acid, anticonvulsants (phenytoin, phenobarbital, etc....), colchicines, and extended-release potassium.
- Large quantities of vitamin C can destroy dibenzozide (1).

Contraindications

None are known.

Comments

Cobalamins are only produced by bacteria and found in food products of animal origins and some fermented vegetable products (4).

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III. Sports and Energy Drinks, Sports Bars, and Gels

Commercially available products (Drinks, Bars and Gels) devoted to enhancing athletic performance and recovery are everywhere, and most have not been carefully studied. The most recent literature indicates that prior to exercise, CHO should be the major energy source, whereas after exercise, a combination of CHO and protein should be ingested during the recovery period. A CHO to protein ratio of 4 to 1 has been recommended. In many cases the recommended amino acid mixtures for sustaining and ensuring performance include BCAAs and/or arginine, but a final decision has not been made with respect to the perfect protein. Soy and whey proteins may be the best natural sources of BCAAs, as each contains approximately 18 to 26g of BCAA per 100 g of protein.

A. Fluid Replacement Products

1. Overview of Fluid Replacement Beverages

Sports and energy beverages, although fundamentally similar, serve two different purposes. Both typically contain energy-rich CHOs and other performance-enhancing ingredients, but a sports beverage is intended to maintain hydration. Thus, if the amount of energy (CHO or protein) is too high, hydration status may be compromised by inadequate absorption. The optimum CHO content for a sports drink is between 6% and 8% or 14 to 19 g per 8-oz. serving.

Energy drinks may also contain amino acids. Research shows that BCAAs (leucine, isoleucine and valine) may help regulate serotonin production in the brain and allow extended athletic performance. At present, such studies are few in number, and the exact mechanism for this effect remains unknown. Nevertheless, elite athletes who seek every potential advantage may look to the amino acid content when they choose a sports beverage. Because

extending endurance is a primary goal of energy drinks, athletes would argue for the inclusion of proteins, as most such products appear not to contain them. Future work will determine whether they do confer any such advantage.

2. Types and Composition of Sport and Energy Beverages

Table 2 provides a listing of some popular sport and energy beverages. The two beverages that have a CHO to protein ratio of 4 to 1 are Accelerade and Endurox R4. However, this may not be useful, and could be problematic, except after completing a mission.

Table 2. Composition of Beverages Based on an 8 oz. Serving

Brand Name	Kcal	CHO (g)	Type of CHO	Electrolytes	Other Ingredients
Accelerade	93	20	Sucrose, Maltodextrin, Fructose	Na: 127mg K: 43 mg	Whey Protein, Magnesium, Vitamins C and E
All Sport	70	19-20	High Fructose Corn Syrup	Na: 55 mg K: 55 mg	Niacinamide, Calcium Pantothenate, Thiamine Mononitrate, Pyridoxine Hydrochloride, and Vitamin B ₁₂
CeraSport	76	13	Rice Syrup, Sucrose	Na: 102 mg K: 37 mg	None
Cytomax	80	15	High Fructose, Corn Syrup, Maltodextrin	Na: 70 mg K: 77 mg 250 mmol/L	L-poly lactate, Vitamin C, Succinate
Endurox R4	93	17	Complex CHO, Glucose, Crystalline Fructose	Na: 78 mg K: 47 mg	Vitamin C and E, Calcium, Iron, Protein, Magnesium, L-arginine, Ciwujia, L-glutamine
G-Push G1 Hydration Formula	25	6	Galactose	Na: 170 mg K: 40 mg	Vitamins A and C
Gatorade	50	14	Sucrose, Glucose, Fructose	Na: 110 mg K: 30 mg	Phosphorous
GU ₂ 0	50	13	Maltodextrin, Fructose	Na: 120 mg K: 20 mg	None
Hydrade	55	10	High Fructose Corn Syrup	Na: 91 mg K: 77 mg	Vitamin C, Glycerol,
Metabolol Endurance	133	16	Maltodextrin, Fructose	Na: 140 mg K: 200 mg	Everything Possible!!
Met-Rx ORS	75	19	Fructose, Glucose	Na: 125 mg K: 40 mg	None
Orange Juice	112	28	Fructose Glucose Sucrose	Na: 2.8 mg K: 510 mg 690 mOsm	Calcium, Niacin, Iron, Vitamins A and C, Thiamin, Riboflavin Phosphorous,

Table 2. Composition of Beverages Based on an 8 oz. Serving

Brand Name	Kcal	CHO (g)	Type of CHO	Electrolytes	Other Ingredients
Powerade	72	19	High Fructose, Corn Syrup, Maltodextrin	Na: 53 mg K: 33 mg	B Vitamins: (Niacin, B ₆ , and B ₁₂)
Pro-Hydrator	0	0	No CHO	Na: 2.5 mg K: 4.5 mg	Glycerol
Revenge Sport	50	10	Maltodextrin, Fructose, Glucose	Na: 48 mg K: 80 mg	Vitamins C and E, Glutamine, Ribose, Succinates, Citrates, Chromium
Ultima	16	4	Maltodextrin	Na: 8 mg K: 16 mg	Ester C, Thiamine, Folic Acid, B ₆ , B ₁₂ , Riboflavin, Magnesium, Choline, Grape Seed Extract, CoQ ₁₀ , Selenium
Water	-	-	-	low	

3. Concerns

Unless one reads the small print for currently marketed fluid replacement beverages, any of a number of “other ingredients” may be ingested without knowing it. For example, Endurox 4 contains “Ciwujia”, also known as Siberian Ginseng. Ciwujia is promoted as helping to reduce fatigue associated with endurance exercise and is actually sold under the name: “Endurox”. A web site for Endurox (<http://endurox.com>) provides information about the product. Another product “Ultima” contains a plethora of other ingredients, to include choline, grape seed extract, CoQ₁₀, and selenium. If one were to drink a lot of this product, toxic amounts of the nutrients could easily be ingested.

B. Sports Bars

1. Overview of Sports Bars

Sports bars are popular because they offer convenient, pre-packaged food that is potentially good and nutritious. However, a number of important issues should be considered for such bars. First, they shouldn't be eaten right before a strenuous workout, as stomach problems could ensue. Sports bars require digestion to be effective.

Although most original sports bars were developed to provide an easily accessible source of CHO, many bars now provide complex proteins and may be high in fat. These bars are for other purposes, such as a meal at least two hours prior to an event, because it will take about two hours to digest, or right after an event for recovery. If sports bars are to be used, knowledge about nutritional needs is important. For example, if a CHO is needed, then a bagel, cereal, fruits, and fruit beverages are cheaper than pre-packaged foods. However, prior to and during missions and training, sports bars are exceptional for maintaining performance standards over a longer time period.

Not all bars are created equally: they vary in the type and amount of CHO, energy, protein and fat. Some sports bars provide only 150 calories (Tiger's Milk), whereas others provide up to 340 calories (Met-Rx). Additionally, some bars are composed primarily of CHOs, while others contain more protein -- and sometimes a moderate dose of fat that you might not need. Since CHOs are the primary nutrient required by working muscles, it is most reasonable to eat a CHO-heavy sports bar before exercising. Most importantly, many contain more than just “energy-providing” nutrients. Reading the label is important. Also, if one lives by the 4 to 1 ratio for CHO to protein, only one of the bars comes close to this goal.



2. Types and Composition of Sports Bars

Table 3 provides a listing of some of the more popular sports bars.

Table 3. Composition of Nutritional Bars: Ordered by% of Energy Derived from Carbohydrate

Brand Name	Energy (kcal)	CHO (% of kcal)	Fat (% of kcal)	Protein (% of kcal)	Protein (g)	CHO to Protein Ratio
PowerBar	230	78	11	11	9	5.0
Gatorade Energy Bar	250	75	18	7	6	7.8
Clif Bar	240	68	8	20	12	3.4
Luna Bar	170	64	13	23	10	2.7
Think Divine	200	64	30	6	6	5.3
GeniSoy	220	60	14	26	14	2.4
Met-Rx	340	57	10	33	27	1.8

Table 3. Composition of Nutritional Bars: Ordered by % of Energy Derived from Carbohydrate

Brand Name	Energy (kcal)	CHO (% of kcal)	Fat (% of kcal)	Protein (% of kcal)	Protein (g)	CHO to Protein Ratio
Bioprotein Bar	290	55	16	29	21	1.9
Tiger s Milk	150	48	40	12	6	3.0
ZonePerfect	200	48	30	22	14	1.7
Balance Bar	200	44	25	31	14	1.6
Sugar-Free ProteinPlus	180	42	25	33	16	1.2
Ironman Triathlon Bar	230	40	30	30	16	1.4
Atkins Advantage Bar	218	31	54	15	18	0.9
Detour Bar	290	29	25	46	32	0.7
Low Carb Keto-Bar	200	28	23	49	24	0.1
PremierNutrition Bar	280	28	26	46	30	0.1
Protein Revolution Low Carb Bar	230	4	30	38	22	0.1
Ultimate Low-Carb Bar	230	4	22	40	23	
Metabolift Bar	120	3	29	40	12	

3. Claims by Sports Bar Manufacturers

Being aware of claims for the various sports bars is important for understanding and comparing the products. Below are selected claims put forward by various manufacturers.

Atkins Advantage Bar

It is designed for “on-the-go” Atkins followers and can be used as a meal-replacement or a snack. In addition to being low-CHO, it features 40-70% of the Recommended Daily Intakes (RDI) for vitamin C, calcium, zinc, and folic acid, as well as omega-3 and omega-6 fatty acids.

Balance Bar

The Balance bar, based on the Zone’s 40-30-30 principle, promises complete and balanced nutrition and is marketed as a nutritious snack.

Bioprotein Bar

The Bioprotein bar is high in protein. It is advertised to provide 35% of 19 essential vitamins and minerals. This bar is most likely just an expensive source of protein, but may be useful after strenuous mission. They claim that eating these bars will maximize training and enhance recovery.

Clif Bar

Clif Bar, designed as a more “homemade” version of a classic energy bar, contains premium, minimally processed ingredients and is free from wheat and dairy: it is targeted primarily to the basic outdoor enthusiast or generally busy person. It claims to keep blood sugar levels constant, without causing a sugar crash. Because it is made of soluble and insoluble fibers, it helps slow the absorption of sugar and create more sustained energy. They are prepared like dense granola cookies with chunks of dried fruit and nuts.

Detour Bar

The Detour bar is advertised as being the first protein-energy bar with whey protein. It is very high in protein, but also contains riboflavin, folic acid, vitamin B12, calcium, iron, and potassium.

Gatorade Energy Bar

This bar, from The Quaker Oats Company, claims to be a nutritious, great-tasting energy source made from crisp rice and whole-grain rolled oats, while also containing six B vitamins (Thiamin, Riboflavin, Niacin, B6, B12, Pantothenic Acid) and three antioxidants (Vitamins A, C and E).

GeniSoy

This sports bar emphasizes its soy protein content, and is marketed less to athletes and dieters, and more as a general health supplement. GeniSoy bar uses soy protein processed to maintain isoflavones, genestein and daidzein, the compounds considered to be most responsible for the health benefits of soy. Numerous studies have suggested that soy products have the potential to reduce the risk of heart disease, cancer, osteoporosis, and menopause symptoms. It is also boosted with the antioxidants, Vitamin E and selenium.

Ironman Triathlon Bar

Twinlab’s Ironman Triathlon Bar claims that it provides energy to help athletes use their own stored body fat during endurance exercise. This is achieved by featuring “scientifically designed proportions of ingredients” (more protein and fat, and less CHOs, than traditional nutrition bars).

Low Carb Keto-Bar

Low Carb Keto-Bars claim to be the perfect snack for anyone reducing CHO intake and making the switch from fat storage to fat burning. They claim the low CHO content will minimize high blood sugar levels and insulin release; it is specifically designed to fight between-meal-hunger and sweet-cravings. These bars also contain glycerine, glutamine, and medium-chain triglycerides.

Luna Bar

The Luna bar was designed exclusively for women of all ages and physiologic states: there are bars for the pregnant, young and old women. They are promoted as providing adequate folic acid, iron, calcium and protein and should be used to compliment a good diet. Touted as being the “best tasting energy bars ever created”, they provide 170-180 kcal per bar.

Met-Rx

This bar is designed to “enhance endurance and recovery” and emphasizes that it is not just an energy bar or snack, but “a convenient way to ensure a steady supply of protein, vitamins, and minerals throughout the day.” It provides 100% of the RDI for calcium.

Metabolift Bar

The bars from Metabolift may be a problem. Not only do they contain many food-like ingredients, including various forms of protein (casein, soy protein isolate, hydrolyzed gelatin, whey protein isolate, and other milk proteins), it also contains MaHuang extract (Ephedra Alkaloids), Guarana Seed extract (caffeine), Siberian Ginseng Root Extract, Green Tea Leaf extract, ginger root, and citrus bioflavonoids. The manufacturer recommends that it be used as part of a low fat diet and exercise program, but also warns that it should be taken with caution. The claims are that it increases energy, is high in fiber and protein, but low in CHOs. Because of the ephedra and caffeine, this bar is to be avoided.

PowerBar

PowerBar, designed for endurance athletes like runners and cyclists who are working out for 45 minutes or longer, gives instant energy and improves aerobic endurance. The bar is high in CHOs, moderate in protein, and low in fat. It is easy to digest and provides the energy required by athletes to perform to the best of their ability. The company claims their products are researched by using athletes and they will not release a product until athletes are satisfied with the new product.

Premier Nutrition Bar

The Premier Nutrition Bar is higher in protein, and lower in CHO and simple sugars than most other Sports Bars. The Premier Protein Bars are excellent sources of high quality protein in a convenient and compact replacement bar. Each bar contains 30-31 grams of protein and less than 20 grams of CHO. These bars are an easy way to add dietary protein and are good for dieters, athletes, and anyone seeking a high protein snack or meal replacement.

ProteinPlus

This bar is marketed as being “sugar-free”, milk and soy protein blend with 16 essential vitamins and minerals. However, it does contain peanut butter and chocolate, so it is more of a candy bar than anything. If you look at the nutritional content, it is much higher in CHO than most other “protein” bars.

Protein Revolution Low Carb Bar

Protein Revolution Bars from Low Glycemic Technologies are based on a “revolutionary new concept” and claim that “they are good for you and they taste good!” It could be a part of a low-CHO, high-protein diet plan.

Think! Divine

This product is positioned as a healthy version of a candy bar designed to boost mind power with a blend of brain-healthy supplements, such as ginkgo, ginseng, choline, and phosphatidylserine. It is claimed that the bar helps with mental clarity. The bar is 30% fat, with a moderate amount of protein and CHOs, which makes it a handy meal replacement. It can also be eaten before sustained and intense mental activity.

Tiger's Milk

This high-nutrition bar that costs less than most nutrition bars, is promoted as a healthy alternative snack, instead of a candy bar. Tiger's Milk Protein Rich, which resembles a Snickers bar, won the American Taste Award of Excellence in 1999.

Ultimate Low-Carb Bar

Biochem Sports and Fitness Systems' Ultimate Low-Carb Bar is a high-protein, low-CHO snack for athletes featuring 20g of protein vs. 2g of CHO.

ZonePerfect

This bar uses the 40-30-30 profile targeted for Zone Diet enthusiasts. It is designed to do everything the diet does: boost energy, maintain optimum weight and enhance overall health. It also contains omega-3 fatty acids, an essential component of the Zone diet.

C. Energy/Sport GELS

1. Overview of Sport Gels

Sport Gels are a recently developed supplement designed to deliver a substantial amount of CHO in a compact and easily consumed form. Most gels are substantially more concentrated in CHO than sports drinks and provide a large fuel boost in a single serving. However, few persons are aware of the proper way to use and benefit from these gels.

Because all sports gels are rich in CHO, which means they are very slowly absorbed by the body, adequate amounts of water must be consumed. Water dilutes the gel and lowers the osmolality of the combined solution to increase the absorption rate. If inadequate amounts of water are ingested, the combined solution will become hypertonic and inhibit absorption, as well as cause gastrointestinal distress. Drinking an electrolyte replacement drink with the gel (instead of water) will result in improper dilution and slow absorption. This can also lead to stomach irritation and dehydration as cellular fluids are drawn upon to dilute the gel.

Studies indicate similar glycemic responses when compared to liquid or solid foods with the same amount of CHOs. An energy gel composed of 25 grams of CHO taken with 200 ml of fluid was able to maintain blood glucose levels during a two hour run at 70% of $\dot{V}O_{2\max}$ when compared to a placebo. Although it appears that gels may be effective in providing energy for exercise, the biggest challenge may be taking in enough fluid along with them.

2. Types of Carbohydrate Gels

Sport Gels may provide a practical way to carry or consume CHO in a number of sports or military environments. Table 4 provides a comparison of various gels with respect to their CHO content.

Table 4. Examples of Sports Gels Expressed as Amount per 100 Grams

Product (weight)	Energy (kcal)	CHO (g)	Sodium (mg)	Potassium (mg)	Other
e-Gel (57 g)	260	66	386	140	Amino acids, antioxidants, Vitamin B6
GU (32 g)	313	78	125	109	Amino acids, antioxidants, herbal blend, caffeine from cola nut

Table 4. Examples of Sports Gels Expressed as Amount per 100 Grams

Product (weight)	Energy (kcal)	CHO (g)	Sodium (mg)	Potassium (mg)	Other
Power Gel (41 g)	268	63	110	110	Amino acid blend, Vitamins C and E, Caffeine, Kola Nut Extract, Ginseng
Clif Shot (32 g)	312	75	156	156	Magnesium, Caffeine (some flavors),
Hammer Gel (22 g)	413	105	123	--	

Power Gel

PowerGel is a concentrated CHO gel designed to provide athletes with immediate energy during intense athletic activity. It is designed to be used as “fast fuel” during or after intense exercise to replenish glycogen stores.

GU Nutrition Gels

GU gels are energy gels designed for use during exercise. They contain no fiber, fat or protein, but rather are comprised of complex CHOs for rapid absorption and supplying energy to working muscles.

Crank Sports e-Gel

This gel was designed as a complete and balanced energy, hydration and electrolyte replacement. e-Gel is marketed as having more than four times as much sodium and nearly twice as much potassium as the competing gels. Although it does have more sodium, when all gels are expressed in the same units, the advertising does not hold up.

Carb-BOOM Carbohydrate Energy Gel and 6-Pack Energy Gel

Carb-BOOM is a CHO gel made up of concentrated complex CHOs and real fruit. It is marketed as being formulated for easy digestion and fast replenishment of energy during and after strenuous exercise.

Sports Street GU

Sports Street GU is a CHO gel designed to maintain blood glucose, as well as muscle and liver glycogen. It is recommended that GU be taken before, during, and after exercise to maintain energy levels and promotes recovery.

GU Nutrition Gel

This product is specifically formulated to provide energy during exercise. GU Energy Gel contains maltodextrin and fructose with a ratio of 80% complex/20% simple.

Clif Shot

This energy gel comes in five flavors, each with added sodium, potassium, and magnesium. In addition, caffeine is found in two of the five flavors. It is marketed for endurance athletes.

Power Gel

PowerGel is an electrolyte, CHO gel designed for sustaining performance. It comes in seven/eight flavors, three/four of which have caffeine; one of those is double caffeinated. It also contain ginseng, and Kola Nut extract.

Hammer Gel

Unlike many of the other gels, Hammer Gel is sold in a jug with a flask for putting the amount needed into it. It also contains fewer “other agents” than many of the others. It currently comes in seven flavors.

3. Concerns

A number of concerns regarding sport gels have been put forward. These include:

- High cost alternative to other suitable foods and fluids, and should be used only in specific situations for which is it most suited, rather than as a general snack.
- Some brands of gels also contain other compounds such as medium-chain triglycerides (MCT oils) and caffeine.
- Gastrointestinal intolerance may occur due to concentrated CHO load.
- Sports gels should always be consumed with adequate fluid to meet fluid needs.
- Athletes should practice use of gels and assess tolerance during training sessions if they are intended for use during competition.
- May lead to over consumption/over-reliance on low-nutrient CHO sources.

4. Other Types of Gels

Beware as there are a variety of transdermal gels that are used topically for increasing testosterone levels, reducing body fat, and accentuating muscle mass. Some of these include NutraSport Cutting Gel and NutraSport Testroxin Gel.